

Supplemental Online Content

Kuemmel S, Heil J, Bruzas S, et al. Safety of targeted axillary dissection after neoadjuvant therapy in patients with node-positive breast cancer. *JAMA Surg*. Published online June 7, 2023. doi:10.1001/jamasurg.2023.1772

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Abbreviations and the Corresponding Expanded Form

Abbreviation	Expanded Form
ALND	axillary lymph node dissection
aRFI	axillary recurrence-free interval
ART	axillary radiotherapy
BCSS	breast cancer-specific survival
cN+	clinically node-positive
CI	confidence interval
<i>ERBB2</i>	human epidermal growth factor receptor 2 (formerly <i>HER2</i>)
<i>ERBB2+</i>	<i>ERBB2</i> positive
HR	hazard ratio
HR–	hormone receptor negative
HR+	hormone receptor positive
DFS	disease-free survival
LN	lymph node
MARI	Marking Axillary lymph nodes with Radioactive Iodine seeds
NST	neoadjuvant systemic therapy
OS	overall survival
pCR	pathologic complete response
SD	standard deviation
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
TAD	targeted axillary dissection
TLN	target lymph node
TLNB	target lymph node biopsy
TNBC	triple-negative breast cancer
ycN0	clinically node negative after neoadjuvant systemic therapy
ycN+	clinically node positive after neoadjuvant systemic therapy
ypN0	histopathologically node negative after neoadjuvant systemic therapy
ypN+	histopathologically node positive after neoadjuvant systemic therapy
ypT0/Tis	pCR in the breast after neoadjuvant systemic therapy

eTable 2. Baseline Characteristics of All Patients (n = 473) Who Received NST Prior to Surgery, 274 of 473 Patients Who Did Not Undergo TAD, and 199 of 473 Patients Who Underwent Successful TAD

Variable		All patients	No TAD	Successful TAD	P value
		No. (%)	No. (%)	No. (%)	
Patients		473 (100)	274 (100)	199 (100)	
Age (years)	median (range)	53 (25–82)	54 (25–61)	52 (26–82)	.176
ALND	yes	320 (67.7)	240 (87.6)	80 (40.2)	< .001
	no	153 (32.3)	34 (12.4)	119 (59.8)	
Tumor receptor subtype	HR+/ERBB2+	93 (19.7)	54 (19.7)	39 (19.6)	.971
	HR+/ERBB2–	205 (43.3)	118 (43.1)	87 (43.7)	
	HR–/ERBB2+	66 (14.0)	37 (13.5)	29 (14.6)	
	HR–/ERBB2–	109 (23.0)	65 (23.7)	44 (22.1)	
Clinical tumor size at diagnosis (mm)	mean (SD)	28.5 (16.6)	29.9 (18.2)	26.6 (13.9)	.063
	median (range)	2 (1–15)	2 (1–15)	1 (1–9)	< .001
No. of suspicious LNs on ultrasound at diagnosis	1	224 (47.4)	110 (40.1)	114 (57.3)	< .001
	2	113 (23.9)	66 (24.1)	47 (23.6)	
	≥ 3	136 (28.8)	98 (35.8)	38 (19.1)	
Clinical nodal status after NST	ycN0	332 (70.2)	180 (66.0)	152 (76.4)	.014
	ycN+	141 (29.8)	94 (34.0)	47 (23.6)	
Pathological nodal status after NST	ypN0	285 (60.3)	159 (58.0)	126 (63.3)	.255
	ypN+	188 (39.7)	115 (42.0)	73 (36.7)	

Abbreviations: ALND, axillary lymph node dissection; ERBB2, human epidermal growth factor receptor 2; HR–, hormone receptor negative; HR+, hormone receptor positive; LN, lymph node; NST, neoadjuvant systemic therapy; SD, standard deviation; TAD, targeted axillary dissection; ycN0/+, clinically node negative/positive after NST; ypN0/+, pathologically node negative/positive after NST.

eTable 3. Multivariate Cox Regression Analysis for Invasive Disease-Free Survival

	Total	Events N (%)	Multivariate Analysis ^a	
			HR (95% CI)	P
Number	199	28 (14.1)		
Axillary surgery				
TAD + ALND	80 (40.2)	16 (20.0)	1 [Reference]	
TAD	119 (59.8)	12 (10.1)	0.40 (0.10–1.65)	0.203
Age per Year			1.05 (1.01–1.08)	0.008
Tumor receptor subtype				
HR+/ERBB2+	39 (19.6)	3 (7.7)	1 [Reference]	
HR+/ERBB2–	87 (43.7)	14 (16.1)	0.28 (0.06–1.30)	0.104
HR–/ERBB2+	29 (14.6)	3 (10.3)	0.68 (0.21–4.01)	0.675
HR–/ERBB2–	44 (22.1)	8 (18.2)	0.85 (0.20–3.65)	0.832
Clinical tumor size at diagnosis (per mm)			1.03 (1.00–1.05)	0.033
No. of suspicious LNs on ultrasound at diagnosis				
1	114 (57.3)	11 (9.6)	1 [Reference]	
2	47 (23.6)	9 (19.1)	2.19 (0.81–5.91)	0.122
≥ 3	38 (19.1)	8 (21.1)	4.38 (1.48–12.9)	0.008
Clinical nodal status after NST				
ycN0	152 (76.4)	19 (12.5)	1 [Reference]	
ycN+	47 (23.6)	9 (19.1)	1.67 (0.63–4.44)	0.304
Pathological nodal status after NST				
ypN0	126 (63.3)	12 (9.5)	1 [Reference]	
ypN+	73 (36.7)	16 (21.9)	2.48 (0.72–8.60)	0.151
No. of all resected LNs (per LN)			0.97 (0.87–1.07)	0.539
No. of TAD LNs (per LN)			0.78 (0.58–1.04)	0.095
Pathological tumor status after NST				
ypT0	145 (72.9)	13 (9.0)	1 [Reference]	
ypT1–4	50 (25.1)	15 (30.0)	5.70 (2.10–14.4)	<0.001
ypTx	4 (2.0)	0	-	
Radiotherapy				
No	12 (6.0)	3 (25.0)	1 [Reference]	
Yes	180 (90.5)	24 (13.3)	0.13 (0.03–0.53)	0.005
Unknown	7 (3.5)	1 (14.3)	0.61 (0.04–9.82)	0.727
Post-neoadjuvant Chemotherapy				
No	176 (88.4)	27 (15.3)	1 [Reference]	
Yes	17 (8.5)	1 (5.9)	0.37 (0.04–3.12)	0.362
Unknown	6 (3.0)	0	-	

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; ERBB2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; HR–, hormone receptor negative; LN, lymph node; NST, neoadjuvant systemic therapy; TAD, targeted axillary dissection; T, tumor; ycN0/+, clinically node negative/positive after NST; ypN0/+, pathologically node negative/positive after NST.

^a The number of positive lymph nodes had a high intercorrelation with ypN and was therefore excluded from the model. Likewise, endocrine and antibody therapy had a high correlation with tumor receptor subtype and were not included in the model. Statistically significant *P* values are indicated in bold.

eTable 4. Multivariate Cox Regression Analysis for Overall Survival

	Total	Events N (%)	Multivariate Analysis ^a	
			HR (95% CI)	<i>P</i>
Number	199	15 (7.5)		
Axillary surgery				
TAD + ALND	80 (40.2)	8 (10.0)	1 [Reference]	
TAD	119 (59.8)	7 (5.9)	0.68 (0.09–4.85)	0.698
Age per Year			1.05 (1.00–1.11)	0.050
Tumor receptor subtype				
HR+/ <i>ERBB2</i> +	39 (19.6)	2 (5.1)	1 [Reference]	
HR+/ <i>ERBB2</i> –	87 (43.7)	7 (8.0)	0.31 (0.04–2.13)	0.231
HR–/ <i>ERBB2</i> +	29 (14.6)	0	-	
HR–/ <i>ERBB2</i> –	44 (22.1)	6 (13.6)	2.75 (0.49–15.5)	0.252
Clinical tumor size at diagnosis (per mm)			1.01 (0.96–1.06)	0.728
No. of suspicious LNs on ultrasound at diagnosis				
1	114 (57.3)	9 (7.9)	1 [Reference]	
2	47 (23.6)	3 (6.4)	0.80 (0.18–3.42)	0.758
≥ 3	38 (19.1)	3 (7.9)	0.98 (0.19–5.01)	0.979
Clinical nodal status after NST				
ycN0	152 (76.4)	7 (4.6)	1 [Reference]	
ycN+	47 (23.6)	8 (17.0)	2.95 (0.92–9.43)	0.069
Pathological nodal status after NST				
ypN0	126 (63.3)	6 (4.8)	1 [Reference]	
≥ ypN1	73 (36.7)	9 (12.3)	3.12 (0.64–15.2)	0.158
No. of all resected LNs (per LN)			1.01 (0.86–1.18)	0.931
No. of TAD LNs (per LN)			0.99 (0.69–1.42)	0.952
Pathological tumor status after NST				
ypT0	145 (72.9)	8 (5.5)	1 [Reference]	
ypT1–4	50 (25.1)	6 (12.0)	3.06 (0.78–12.0)	0.110
ypTx	4 (2.0)	1 (25.0)	-	
Radiotherapy				
No	12 (6.0)	2 (16.7)	1 [Reference]	
Yes	180 (90.5)	12 (6.7)	0.30 (0.05–1.74)	0.178
Unknown	7 (3.5)	1 (14.3)	-	
Post-neoadjuvant Chemotherapy				
No	176 (88.4)	14 (8.0)	1 [Reference]	
Yes	17 (8.5)	0	-	
Unknown	6 (3.0)	1 (16.7)	-	

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; *ERBB2*, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; HR–, hormone receptor negative; LN, lymph node; NST, neoadjuvant systemic therapy; TAD, targeted axillary dissection; T, tumor; ycN0/+, clinically node negative/positive after NST; ypN0/+, pathologically node negative/positive after NST.

^a The number of positive lymph nodes had a high intercorrelation with ypN and was therefore excluded from the model. Likewise, endocrine and antibody therapy had a high correlation with tumor receptor subtype and were not included in the model. Statistically significant *P* values are indicated in bold.

eTable 5. Multivariate Cox Regression Analysis for Distant Disease-Free Survival

	Total	Events	Multivariate Analysis ^a	
			HR (95% CI)	P
Number	199	24 (12.1)		
Axillary surgery				
TAD + ALND	80 (40.2)	15 (18.8)	1 [Reference]	
TAD	119 (59.8)	9 (7.6)	0.25 (0.05–1.15)	0.076
Age per Year			1.04 (0.99–1.08)	0.080
Tumor receptor subtype				
HR+/ <i>ERBB2</i> +	39 (19.6)	3 (7.7)	1 [Reference]	
HR+/ <i>ERBB2</i> –	87 (43.7)	13 (14.9)	0.16 (0.03–0.82)	0.028
HR–/ <i>ERBB2</i> +	29 (14.6)	2 (6.9)	0.40 (0.05–3.29)	0.395
HR–/ <i>ERBB2</i> –	44 (22.1)	6 (13.6)	0.58 (0.21–2.80)	0.498
Clinical tumor size at diagnosis (per mm)			1.03 (1.00–1.06)	0.024
No. of suspicious LNs on ultrasound at diagnosis				
1	114 (57.3)	10 (8.8)	1 [Reference]	
2	47 (23.6)	8 (17.0)	2.17 (0.75–6.27)	0.152
≥ 3	38 (19.1)	6 (15.8)	4.63 (1.35–15.8)	0.015
Clinical nodal status after NST				
ycN0	152 (76.4)	15 (9.9)	1 [Reference]	
ycN+	47 (23.6)	9 (19.1)	2.31 (0.82–6.53)	0.114
Pathological nodal status after NST				
ypN0	126 (63.3)	8 (6.3)	1 [Reference]	
≥ ypN1	73 (36.7)	16 (21.9)	3.69 (0.94–14.5)	0.062
No. of all resected LNs (per LN)			0.93 (0.84–1.04)	0.212
No. of TAD LNs (per LN)			0.75 (0.53–1.06)	0.100
Pathological tumor status after NST				
ypT0	145 (72.9)	9 (6.2)	1 [Reference]	
ypT1–4	50 (25.1)	15 (30.0)	8.23 (2.71–25.0)	<0.001
ypTx	4 (2.0)	0	-	
Radiotherapy				
No	12 (6.0)	2 (16.7)	1 [Reference]	
Yes	180 (90.5)	21 (11.7)	0.19 (0.03–1.02)	0.053
Unknown	7 (3.5)	1 (14.3)	0.17 (0.01–3.91)	0.267
Post-neoadjuvant Chemotherapy				
No	176 (88.4)	23 (13.1)	1 [Reference]	
Yes	17 (8.5)	1 (5.9)	0.38 (0.05–3.28)	0.381
Unknown	6 (3.0)	0	-	

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; *ERBB2*, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; HR–, hormone receptor negative; LN, lymph node; NST, neoadjuvant systemic therapy; TAD, targeted axillary dissection; T, tumor; ycN0/+, clinically node negative/positive after NST; ypN0/+, pathologically node negative/positive after NST.

^a The number of positive lymph nodes had a high intercorrelation with ypN and was therefore excluded from the model. Likewise, endocrine and antibody therapy had a high correlation with tumor receptor subtype and were not included in the model. Statistically significant *P* values are indicated in bold.

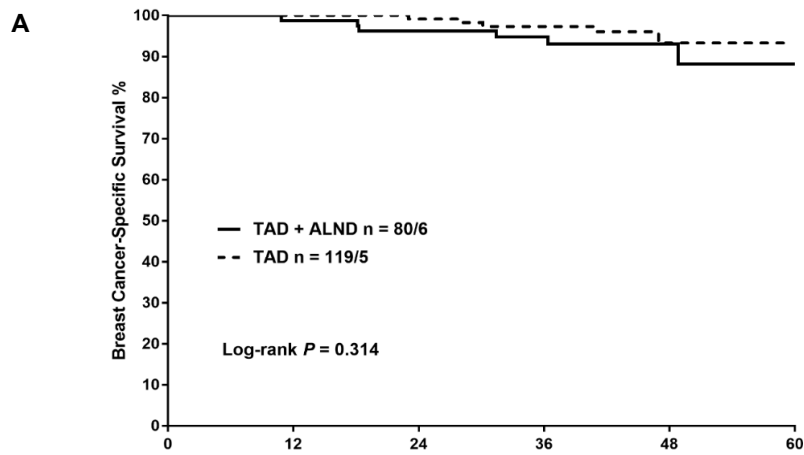
eTable 6. Multivariate Cox Regression Analysis for Breast Cancer-Specific Survival

	Total	Events N (%)	Multivariate Analysis ^a	
			HR (95% CI)	P
Number	199	11 (5.5)		
Axillary surgery				
TAD + ALND	80 (40.2)	6 (7.5)	1 [Reference]	
TAD	119 (59.8)	5 (4.2)	1.05 (0.09–11.7)	0.968
Age per Year			1.09 (1.02–1.17)	0.017
Tumor receptor subtype				
HR+/ <i>ERBB2</i> +	39 (19.6)	2 (5.1)	1 [Reference]	
HR+/ <i>ERBB2</i> –	87 (43.7)	5 (5.7)	0.31 (0.04–2.13)	0.231
HR–/ <i>ERBB2</i> +	29 (14.6)	0	-	
HR–/ <i>ERBB2</i> –	44 (22.1)	4 (9.1)	1.75 (0.27–11.3)	0.557
Clinical tumor size at diagnosis (per mm)			1.00 (0.94–1.07)	0.932
No. of suspicious LNs on ultrasound at diagnosis				
1	114 (57.3)	7 (6.1)	1 [Reference]	
2	47 (23.6)	3 (6.4)	1.78 (0.37–8.57)	0.573
≥ 3	38 (19.1)	2 (2.6)	0.38 (0.20–7.71)	0.529
Clinical nodal status after NST				
ycN0	152 (76.4)	6 (3.9)	1 [Reference]	
ycN+	47 (23.6)	5 (10.6)	2.41 (0.56–10.4)	0.240
Pathological nodal status after NST				
ypN0	126 (63.3)	3 (2.4)	1 [Reference]	
≥ ypN1	73 (36.7)	8 (11.0)	10.1 (1.36–74.6)	0.024
No. of all resected LNs (per LN)			1.02 (0.85–1.22)	0.807
No. of TAD LNs (per LN)			0.71 (0.39–1.30)	0.269
Pathological tumor status after NST				
ypT0	145 (72.9)	5 (3.4)	1 [Reference]	
ypT1-4	50 (25.1)	6 (12.0)	3.94 (0.86–18.1)	0.078
ypTx	4 (2.0)	0	-	
Radiotherapy				
No	12 (6.0)	2 (16.7)	1 [Reference]	
Yes	180 (90.5)	9 (5.0)	0.10 (0.01–0.79)	0.030
Unknown	7 (3.5)	0	-	
Post-neoadjuvant Chemotherapy				
No	176 (88.4)	11 (6.3)	1 [Reference]	
Yes	17 (8.5)	0	-	
Unknown	6 (3.0)	0	-	

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; *ERBB2*, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor positive; HR–, hormone receptor negative; LN, lymph node; NST, neoadjuvant systemic therapy; TAD, targeted axillary dissection; T, tumor; ycN0/+, clinically node negative/positive after NST; ypN0/+, pathologically node negative/positive after NST.

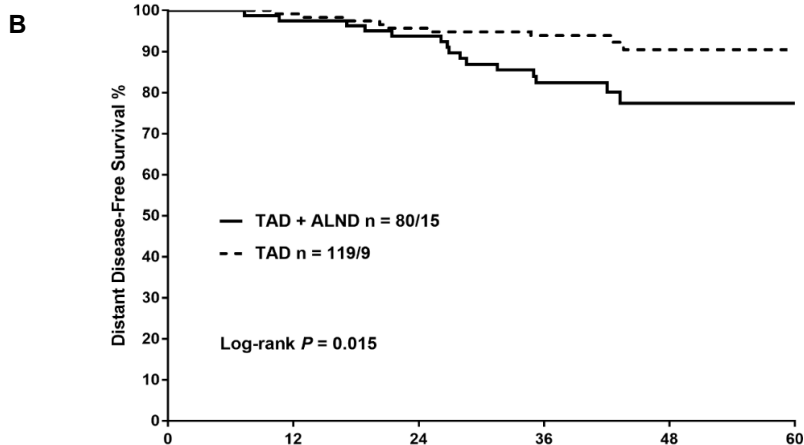
^a The number of positive lymph nodes had a high intercorrelation with ypN and was therefore excluded from the model. Likewise, endocrine and antibody therapy had a high correlation with tumor receptor subtype and were not included in the model. Statistically significant *P* values are indicated in bold.

eFigure. Kaplan-Meier Curves for Distant Disease-Free Survival, Breast Cancer–Specific Survival, and Locoregional Recurrence



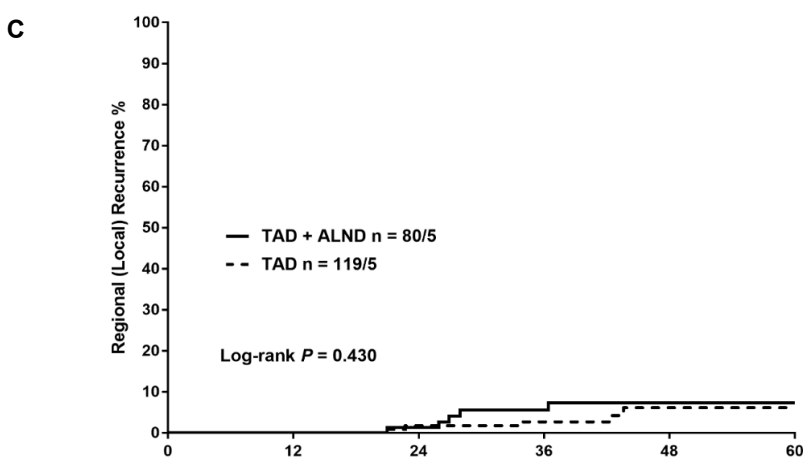
No. at risk:

	0	12	24	36	48	60
TAD	119	118	114	104	31	
TAD + ALND	80	79	74	59	24	



No. at risk:

	0	12	24	36	48	60
TAD	119	117	109	99	29	
TAD + ALND	80	78	72	53	22	



No. at risk:

	0	12	24	36	48	60
TAD	119	118	113	102	28	
TAD + ALND	80	79	73	57	24	

Kaplan-Meier curves for (A) breast-cancer specific survival, (B) distant disease-free survival as well as cumulative incidence of (C) locoregional recurrence for 80 patients who underwent targeted axillary dissection (TAD) with axillary lymph node dissection (ALND) versus 119 patients who underwent TAD alone. Fifteen patients in the TAD with ALND group and six patients in the TAD alone group suffered from distant metastases; six and five patients, respectively, died of breast cancer. All 10 patients, five in each group, with regional recurrence suffered from local recurrence as well.