Supplementary Online Content

Goodman CR, Seagle B-L L, Friedl TWP, et al. Association of circulating tumor cell status with benefit of radiotherapy and survival in early-stage breast cancer. *JAMA Oncol*. Published online May 3, 2018. doi: 10.1001/jamaoncol.2018.0163

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

eMethods. Participants, Materials, Outcomes, and Analysis

National Cancer Database

Individual-level data is prospectively collected by professional registrars and is audited. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each Commission on Cancer-accredited hospital.

SUCCESS Trial

The Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treatment, as well as Extended Bisphosphonate and Surveillance (SUCCESS) trial was a prospective randomized Phase III trial (EUDRA-CT No. 2005-000490-21).

Eligible patients included women with pT1-T4, pN0-N3, M0 breast cancer considered to be average- or high-risk for whom chemotherapy was recommended. All women had at least one of the following high-risk factors: histopathological proof of axillary lymph node metastases (pN1-3), tumor size ≥pT2, histological grade 3, negative hormone receptor status, or age ≤35 years. Women were randomized to receive adjuvant fluorouracil-epirubicin-cylcophosphamide (FEC; 500/100/500mg/m^2) followed by three cycles of docetaxel (100mg/m^2) every 3 weeks or three cycles of FEC followed by 3 cycles of gemcitabine (1000mg/m^2 d1,8)-docetaxel (75mg/m^2) every 3 weeks.[7] Following the completion of chemotherapy, the patients were further randomized to receive either 2 or 5 years of zoledronate.

Surgery consisted of either breast conserving surgery (BCS) or mastectomy with R0 resection. Sentinel node dissection was performed in all patients without clinical evidence of nodal disease followed by complete axillary node dissection in patients with positive sentinel nodes. Patients with clinical evidence of nodal disease received axillary lymph node dissection. Radiotherapy consisted of treatment of the breast or chest wall using tangential opposition beams to a total dose of 50.4 Gy in 1.8 Gy daily fractions. A boost was given at the discretion of the individual investigator. Irradiation of the axillary lymph nodes was not permitted for patients with three or less positive lymph nodes.

Detection of CTCs

SUCCESS trial: Following resection, but prior to adjuvant therapy, blood was collected for identification of CTCs on 1,994 patients using the CellSearch system®.[19] CTCs were evaluated using the CellSearch System (Veridex, Raritan, NJ) as previously reported.[1] Thirty (30) milliliters of peripheral blood was collected into three CellSave tubes, and 7.5mL of the centrifuged buffy coat was processed. The samples with at least one positive CTC per 30mL of peripheral blood collected was considered CTC-positive.

Variable Definition

Variables were defined as follows: Lymphovascular Invasion (LVI): "Negative," or "Positive." Histology: ductal ("IDC"), lobular or mixed ("ILC/Mixed"), or "Other." Type of surgery: breast conserving surgery ("BCS"), or mastectomy "Mastectomy." Race: "White" or "Black/Other." Hispanic ethnicity: "No" or "Yes." Insurance status: "Private", "Government," or "None." Charlson-Deyo comorbidity score: "0", "1", or "2". Prior cancer: "No" or "Yes." Facility type: "Academic," "Community", "Comprehensive," or "Integrated." Income quartile, defined by NCDB based on the median household income within the patient's zip code: Top", "2nd", "3rd", "Bottom." Education quartile, defined by NCDB based on the number of adults in the patient's zip code who did not graduate from high school: "Top", "2nd", "3rd", "Bottom." Population: "Urban" or "Nonurban." Menopausal status: "Pre-menopausal" or "Post-menopausal." A new variable was made combining CTC-status and radiotherapy. All variables were checked for consistency. Missing data was coded as "Unknown."

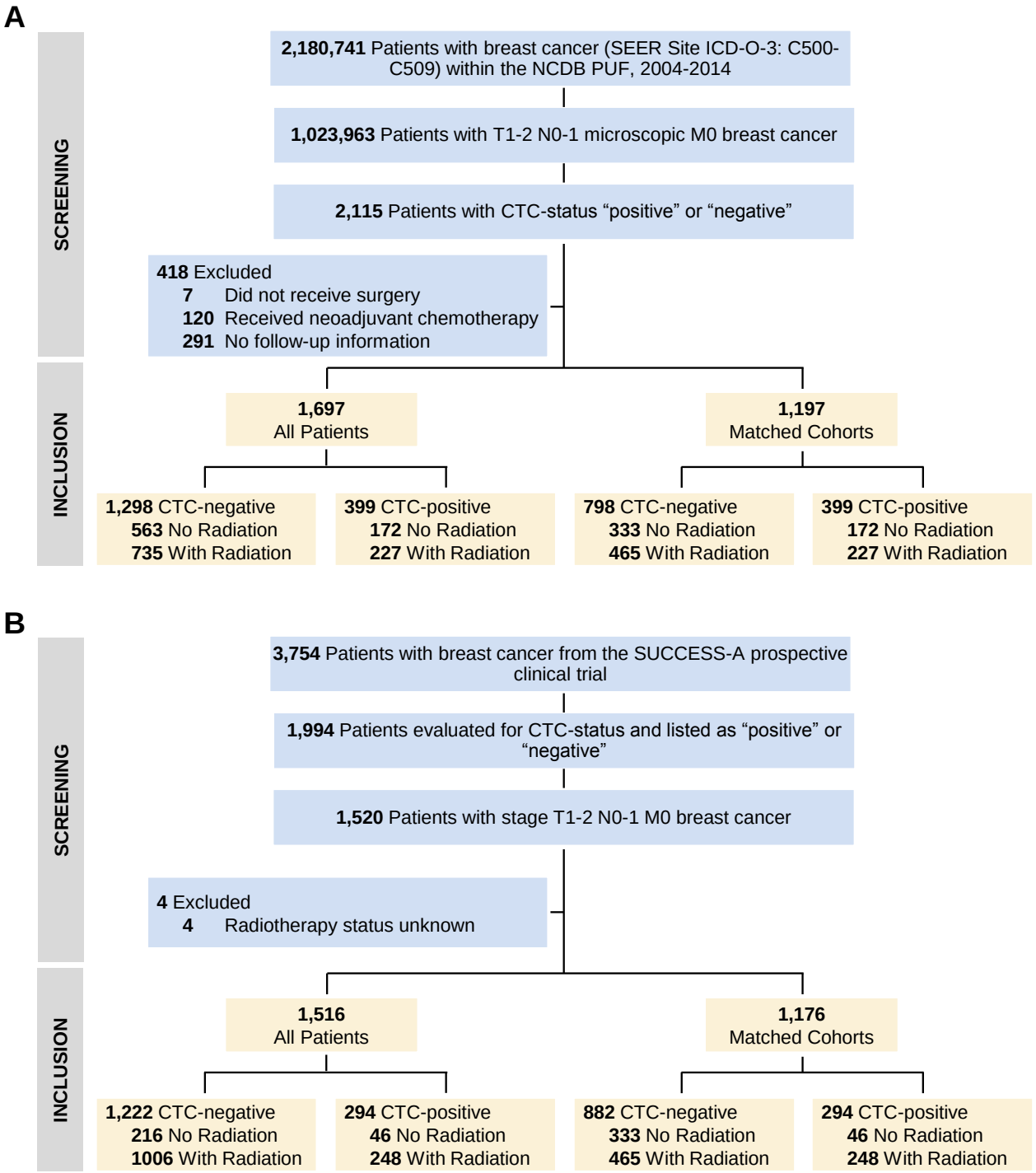
Definition of Outcomes

Local Recurrence-Free Survival (LRFS) and Disease-Free Survival (DFS) were defined as per the SUCCESS trial. LRFS was defined as any relapse in the area of surgery between the sternum and anterior axillary line below the inferior clavicular fossa and above the 7th rib, including involvement of the pectoral muscles, serratus lateralis muscles, or the oblique externus muscle. DFS was defined as invasive disease recurrence, second primary tumors, and death from any cause.

Multivariable Models

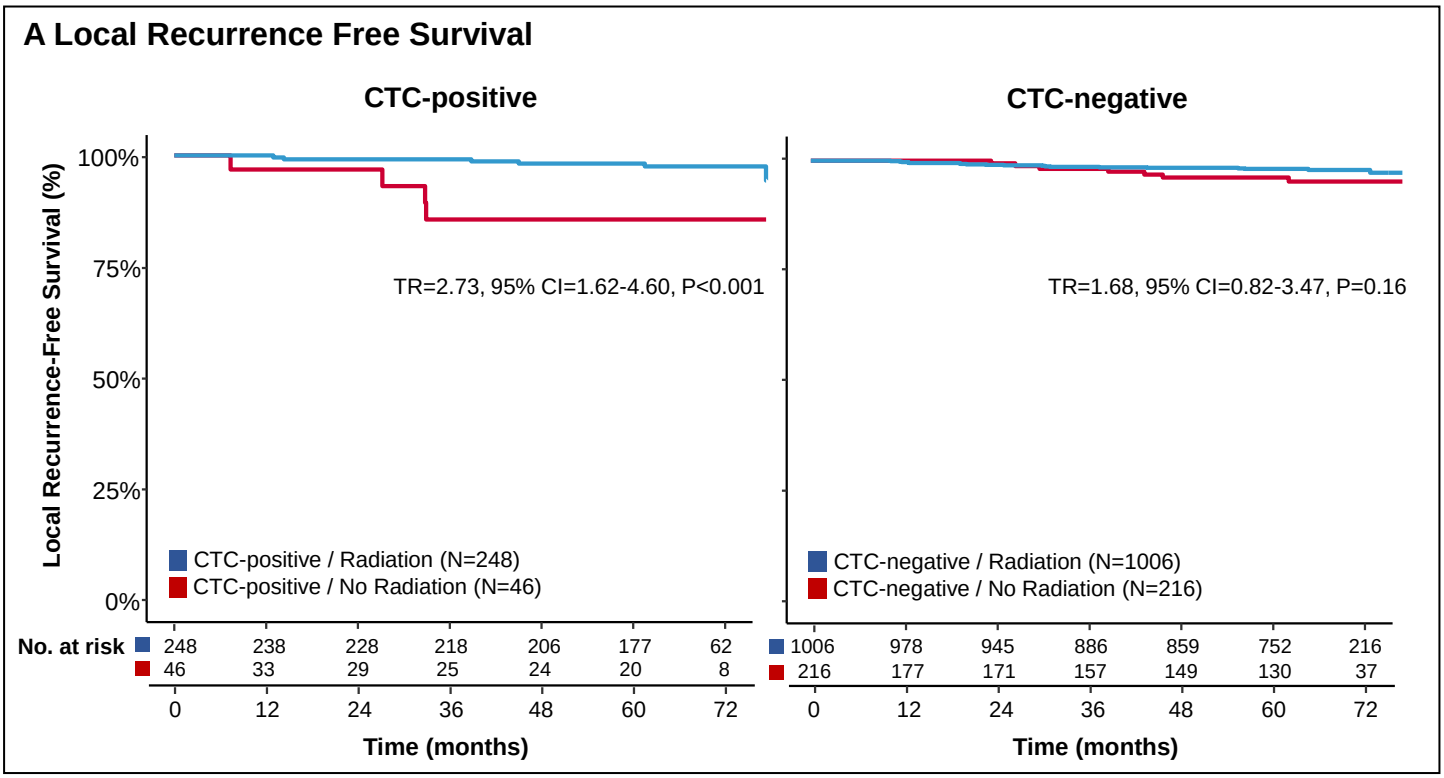
In each multivariable analysis, inclusion of CTC-status as a covariate led to decreased Akaike Information Criterion (AIC) values, indicating that inclusion of CTC improves the model compared to a model in which radiotherapy alone is considered, while inclusion of the interaction variable decreased AIC values yet further.

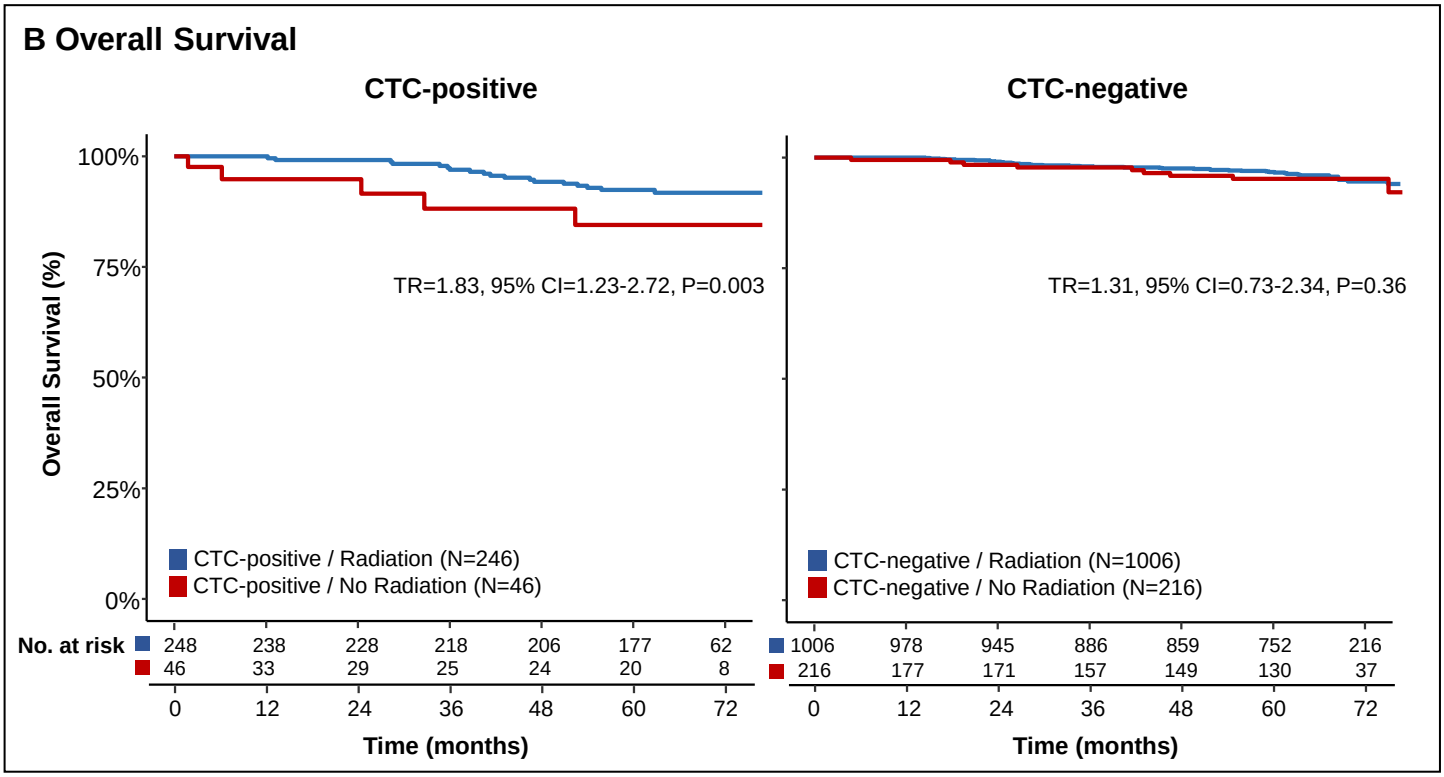
eFigure 1. CONSORT Diagram of Patient Selection Within the (A) National Cancer Database (NCDB), 2004 to 2014, and (B) SUCCESS clinical trial.



ICD: International Classification of Diseases; PUF: Participant user file; CTC: Circulating tumor cell; RT: Radiotherapy.

eFigure 2. Unadjusted Survival Curves for the SUCCESS Cohorts





Unadjusted survival curves based on Kaplan-Meier estimates for CTC-positive (left) and CTC-negative (right) patients with primary breast cancer treated with (blue) or without (red) adjuvant radiotherapy from the SUCCESS cohort for (A) local recurrence-free survival and (B) overall survival. TR=Time ratio; 95% CI = 95% Confidence Interval; P: P-value; CTC: Circulating tumor cell.

eTable 1. Characteristics of the Matched Cohorts of All Patients From the NCDB Cohort Grouped by CTC Status

Variable	CTC-negative (N=798)	CTC-positive (N=399)	P Value	SMD
Age (years)	62.0 [52.0, 70.0]	61.0 [52.0, 70.0]	.63	0.03
Follow-up (mo)	39.2 [26.6, 52.3]	40.4 [28.7, 54.0]	.15	0.09
Tumor stage				
1	596 (74.7)	290 (72.7)	.49	0.05
2	202 (25.3)	109 (27.3)		
Nodal stage				
0	747 (93.6)	366 (91.7)	.23	0.07
1 (microscopic)	51 (6)	33 (8)		
Grade				
1	247 (31.0)	124 (31.1)	>.99	0.003
2	356 (44.6)	178 (44.6)		
3	195 (24.4)	97 (24)		
LVI				
Negative	582 (72.9)	287 (71.9)	.44	0.08
Positive	76 (10)	47 (12)		
Unknown	140 (17.5)	65 (16)		
Histology				
IDC	621 (77.8)	311 (77.9)	>.99	0.003
ILC/Mixed	177 (22.2)	88 (22)		
ER status				
Positive	728 (91.2)	365 (91.5)	.91	0.01
Negative	70 (9)	34 (9)		
PR status				
Positive	649 (81.3)	324 (81.2)	>.99	0.003
Negative	149 (18.7)	75 (19)		
ERBB2 status				
Negative	705 (88.3)	345 (86.5)	.35	0.06
Positive	93 (12)	54 (14)		
Surgery				
BCS	478 (59.9)	241 (60.4)	.90	0.01
Mastectomy	320 (40.1)	158 (39.6)		
Chemotherapy				
No	571 (71.6)	279 (69.9)	.59	0.04
Yes	227 (28.4)	120 (30.1)		
Radiotherapy				
No	342 (42.9)	172 (43.1)	.95	0.01
Yes	456 (57.1)	227 (56.9)		
Hormone therapy				
No	171 (21.4)	86 (22)	>.99	0.003
Yes	627 (78.6)	313 (78.4)		
Race				
White	623 (78.1)	316 (79.2)	.71	0.03
Black/Other	175 (21.9)	83 (21)		
Hispanic				
No	760 (95.2)	378 (94.7)	.78	0.02
Yes	38 (5)	21 (5.3)		
Insurance status				
Private	396 (49.6)	195 (48.9)	.85	0.02
Government/None	402 (50.4)	204 (51.1)		
Comorbidity score				
0	696 (87.2)	346 (86.7)	.89	0.03
1	86 (11)	46 (12)		
2	16 (2)	7 (2)		

Variable	CTC-negative (N=798)	CTC-positive (N=399)	P Value	SMD
Prior cancer				
No	635 (79.6)	310 (77.7)	.45	0.05
Yes	163 (20.4)	89 (22.3)		
Facility type				
Academic	275 (34.5)	133 (33.3)		
Community	96 (12)	52 (13)	.95	0.04
Comprehensive	361 (45.2)	182 (45.6)		
Integrated	66 (8)	32 (8)		
Income quartile				
Top	288 (36.1)	138 (34.6)		
2nd	197 (24.7)	102 (25.6)	.96	0.03
3rd	183 (22.9)	92 (23)		
Bottom	130 (16.3)	67 (17)		
Education quartile				
Top	218 (27.3)	108 (27.1)		
2nd	244 (30.6)	123 (30.8)	.99	0.02
3rd	221 (27.7)	108 (27.1)		
Bottom	115 (14.4)	60 (15)		
Region				
Nonurban	74 (9)	39 (10)	.83	0.02
Urban	724 (90.7)	360 (90.2)		

Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher's exact test or Kruskal-Wallis test. P: P-value; SMD: Standardized Mean Difference; CTC: Circulating tumor cell; Follow-up (mo): Follow-up (months); LVI: Lymphovascular Invasion; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma, ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2; BCS: Breast-conserving surgery.

eTable 2. Characteristics of the Matched Cohorts of Patients From the SUCCESS Cohort Grouped by CTC Status

Variable	CTC-negative (N=882)	CTC-positive (N=294)	P Value	SMD
Age (years)	53.0 [46.0, 61.0]	54.0 [45.0, 61.0]	.81	<0.001
Follow-up (mo)	64.4 [60.0-69.9]	64.2 [59.6-72.1]	.85	0.03
Grade				
1	34 (4)	11 (4)	>.99	0.006
2	414 (46.9)	138 (46.9)		
3	434 (49.2)	145 (49.3)		
Tumor stage				
1	390 (44.2)	128 (43.5)	.89	0.01
2	492 (55.8)	166 (56.5)		
Nodal stage				
0	380 (43.1)	127 (43.2)	>.99	0.002
1*	502 (56.9)	167 (56.8)		
Histology				
IDC	730 (82.8)	242 (82.3)	.91	0.03
ILC	89 (10)	29 (10)		
Other	63 (7)	23 (8)		
ER status				
Positive	616 (69.8)	205 (69.7)	>.99	0.002
Negative	266 (30.2)	89 (30)		
PR status				
Positive	580 (65.8)	195 (66.3)	.89	0.01
Negative	302 (34.2)	99 (34)		
ERBB2 status				
Negative	648 (73.5)	219 (74.5)	.88	0.02
Positive	216 (25)	70 (24)		
Menopausal status				
Pre-menopausal	379 (43.0)	124 (42.2)	.84	0.02
Post-menopausal	503 (57.0)	170 (57.8)		
Chemotherapy				
FEC-Doc	415 (47.1)	141 (48.0)	.79	0.02
FEC-DocG	467 (52.9)	153 (52.0)		
Radiotherapy				
Yes	739 (83.8)	248 (84.4)	.86	0.02
No	143 (16.2)	46 (16)		
Hormone therapy				
Yes	638 (72.3)	210 (71.4)	.76	0.02
No	244 (27.7)	84 (29)		
Surgery				
BCS	657 (74.5)	219 (74.5)	>.99	<0.001
Mastectomy	225 (25.5)	75 (26)		
Trastuzumab				
No	694 (78.7)	234 (79.6)	.80	0.02
Yes	188 (21.3)	60 (20)		

Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher's exact test or Kruskal-Wallis test. P: P-value; SMD: Standardized Mean Difference; CTC: Circulating tumor cell; Follow-up (mo): Follow-up (months); IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma, ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2; FEC-Doc: fluorouracil-epirubicin-cylcophosphamide followed by docetaxel; FEC-DocG: fluorouracil-epirubicin-cylcophosphamide followed by gemcitabine-docetaxel. *includes N1mi (microscopic) and N1.

eTable 3. Characteristics of the Matched Cohorts of Patients Who Underwent Breast-Conserving Surgery From the Pooled Cohort

Variable	CTC-negative (N=1380)	CTC-positive (N=460)	P Value	SMD
Age (years)	58.0 [49.0, 67.0]	58.0 [50.0, 66.0]	.97	<0.001
Follow-up (mo)	58.5 [34.4, 65.0]	56.6 [33.7, 64.9]	.76	0.02
Grade				
1	225 (16.3)	75 (16)	>.99	0.005
2	654 (47.4)	219 (47.6)		
3	501 (36.3)	166 (36.1)		
Tumor stage				
1	858 (62.2)	292 (63.5)	.66	0.03
2	522 (37.8)	168 (36.5)		
Nodal stage				
0	973 (70.5)	322 (70.0)	.88	0.01
1*	407 (29.5)	138 (30.0)		
Histology				
IDC	1115 (80.8)	367 (79.8)	.63	0.03
ILC/Mixed	265 (19.2)	93 (20)		
ER status				
Positive	1074 (77.8)	364 (79.1)	.60	0.03
Negative	306 (22.2)	96 (21)		
PR status				
Positive	1000 (72.5)	339 (73.7)	.63	0.03
Negative	380 (27.5)	121 (26.3)		
ERBB2 status				
Negative	1160 (84.1)	387 (84.1)	>.99	0.002
Positive	220 (15.9)	73 (16)		
Chemotherapy				
No	492 (35.7)	168 (36.5)	.74	0.02
Yes	888 (64.3)	292 (63.5)		
Radiotherapy				
Yes	1233 (89.3)	411 (89.3)	>.99	<0.001
No	147 (10.7)	49 (11)		
Hormone therapy				
Yes	1036 (75.1)	338 (73.5)	.50	0.04
No	344 (24.9)	122 (26.5)		

Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher's exact test or Kruskal-Wallis test. P: P-value; SMD: Standardized Mean Difference; CTC: Circulating tumor cell; Follow-up (mo): Follow-up (months); IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma, ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2. *includes N1mi (microscopic) and N1.

eTable 4. Characteristics of the Matched Cohorts of Patients Who Underwent Mastectomy From the Pooled Cohort

Variable	CTC-negative (N=699)	CTC-positive (N=233)	P Value	SMD
Age (years)	57.0 [49.0, 66.0]	56.0 [48.0, 65.0]	.30	0.09
Follow-up (mo)	39.2 [26.8-52.7]	41.8 [28.5-56.5]	.09	0.12
Grade				
1	127 (18.2)	44 (19)	.87	0.04
2	349 (49.9)	119 (51.1)		
3	223 (31.9)	70 (30)		
Tumor stage				
1	392 (56.1)	126 (54.1)	60	0.04
2	307 (43.9)	107 (45.9)		
Nodal stage				
0	505 (72.2)	171 (73.4)	.80	0.03
1*	194 (27.8)	62 (27)		
Histology				
IDC	551 (78.8)	177 (76.0)	.36	0.07
ILC/Mixed	148 (21.2)	56 (24)		
ER status				
Positive	597 (85.4)	205 (88.0)	.38	0.08
Negative	102 (14.6)	28 (12)		
PR status				
Positive	533 (76.3)	179 (76.8)	.93	0.01
Negative	166 (23.7)	54 (23)		
ERBB2 status				
Negative	583 (83.4)	182 (78.1)	.08	0.14
Positive	116 (16.6)	51 (22)		
Chemotherapy				
No	319 (45.6)	111 (47.6)	.60	0.04
Yes	380 (54.4)	122 (52.4)		
Radiotherapy				
Yes	176 (25.2)	64 (28)	.49	0.05
No	523 (74.8)	169 (72.5)		
Hormone therapy				
Yes	529 (75.7)	186 (79.8)	.21	0.10
No	170 (24.3)	47 (20)		

Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher's exact test or Kruskal-Wallis test. P: P-value; SMD: Standardized Mean Difference; CTC: Circulating tumor cell; Follow-up (mo): Follow-up (months); IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma, ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2. *includes N1mi (microscopic) and N1.

eTable 5. Kaplan-Meier Estimates and Multivariable Survival Models for Overall Survival From the NCDB Cohort

Variable	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Four-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
N (events)					1,697 (92)		1,197 (57)	
Age (per year)					0.97 (0.95-0.98)	<.001	0.97 (0.96-0.98)	<.001
CTC status and RT								
CTC x RT Interaction Coefficient						**.01**		**<.001**
CTC+ RT-	172 (18)	78.6 (74.2-83.0)	88.0 (82.3-94.2)	.005	1 [Reference]		1 [Reference]	
CTC+ RT+	227 (7)	85.5 (83.3-87.6)	94.9 (90.8-99.1)		2.34 (1.26-4.35)	.006	1.66 (1.26-2.17)	<.001
CTC- RT-	563 (34)	82.3 (80.1-84.4)	93.4 (91.1-95.9)		1.93 (1.13-3.30)	.02	1.90 (1.46-2.48)	<.001
CTC- RT+	735 (33)	82.9 (79.5-86.3)	93.9 (91.7-96.1)		1.72 (1.07-2.74)	.02	1.59 (1.23-2.07)	<.001
Grade								
1	467 (24)	97.2 (94.5-100.0)	94.0 (91.3-96.8)	.48	1 [Reference]		1 [Reference]	
2	770 (38)	95.8 (90.8-100.9)	93.3 (91.1-95.6)		1.19 (0.84-1.68)	.33	1.09 (0.87-1.37)	.47
3	460 (30)	95.8 (92.9-98.8)	92.1 (89.0-95.3)		0.85 (0.56-1.31)	.47	0.71 (0.54-0.94)	.01
LVI								
Negative	1275 (68)	67.6 (66.8-68.5)	92.9 (91.1-94.8)	.94	1 [Reference]		1 [Reference]	
Positive	142 (8)	67.8 (65.5-70.0)	92.4 (87.3-97.8)		0.83 (0.51-1.37)	.47	0.87 (0.62-1.21)	.40
Unknown	280 (16)	67.9 (66.3-69.4)	94.9 (91.1-97.8)		0.95 (0.65-1.38)	.78	0.79 (0.63-0.99)	.38
Histology								
IDC	1389 (73)	100.3 (97.0-103.6)	93.5 (91.9-95.1)	.59	1 [Reference]		1 [Reference]	
ILC/mixed	308 (19)	99.6 (95.5-103.8)	91.8 (87.8-96.0)		0.94 (0.65-1.35)	.73	0.81 (0.65-1.01)	.07
Tumor stage								
1	1292 (61)	100.5 (96.5-104.5)	93.7 (92.0-95.5)	.04	1 [Reference]		1 [Reference]	
2	405 (31)	98.3 (94.8-101.9)	91.5 (88.2-94.8)		0.72 (0.51-1.00)	.05	0.85 (0.69-1.05)	.13
Nodal stage								
0	1610 (88)	84.5 (82.8-86.2)	93.1 (91.5-94.7)	.73	1 [Reference]		1 [Reference]	
1 (microscopic)	87 (4)	86.5 (82.7-90.3)	94.1 (88.4-100.0)		0.80 (0.43-1.51)	.50	0.75 (0.48-1.16)	.19
ER status								
Positive	1445 (77)	100.1 (97.0-103.2)	93.4 (91.8-95.1)	.51	1 [Reference]		1 [Reference]	
Negative	252 (15)	101.0 (97.3-104.7)	91.5 (87.1-96.1)		1.21 (0.65-2.24)	.55	1.49 (0.99-2.25)	.06
PR status								
Positive	1274 (67)	101.3 (99.6-103.1)	93.3 (91.6-95.1)	.62	1 [Reference]		1 [Reference]	
Negative	423 (25)	96.5 (86.7-106.2)	92.6 (89.6-95.8)		1.30 (0.83-2.05)	.25	1.17 (0.87-1.59)	.30
ERBB2 status								
Negative	1530 (78)	86.6 (84.5-88.7)	93.4 (91.9-95.1)	.33	1 [Reference]		1 [Reference]	
Positive	167 (12)	86.0 (82.2-89.8	90.6 (85.3-96.3)		0.82 (0.51-1.30)	.40	0.68 (0.48-0.96)	.03
Variable	**Kaplan Meier Estimates**				**Accelerated Failure Time Multivariable Analysis**			

	All Patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Four-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
Hormone therapy								
No	458 (40)	96.7 (93.0-100.4)	88.4 (84.7-92.2)	<.001	1 [Reference]		1 [Reference]	
Yes	1239 (52)	101.4 (98.1-104.8)	94.9 (93.3-96.5)		1.67 (1.16-2.40)	.006	1.41 (1.12-1.77)	.003
Chemotherapy								
No	1181 (71)	100.4 (98.4-102.3)	92.5 (90.6-94.5)	.09	1 [Reference]		1 [Reference]	
Yes	516 (21)	101.1 (95.7-106.6)	94.6 (92.1-97.1)		1.05 (0.72-1.53)	.81	1.15 (0.90-1.47)	.26
Race								
White	1314 (69)	85.8 (83.7-87.8)	93.4 (91.7-95.2)	.50	1 [Reference]		1 [Reference]	
Black/Other	383 (23)	86.6 (84.3-88.8)	92.6 (89.5-95.7)		0.74 (0.53-1.04)	.09	1.12 (0.87-1.43)	.39
Insurance Status								
Private	863 (22)	102.8 (98.7-107.0)	97.1 (95.6-98.6)	<.001	1 [Reference]		1 [Reference]	
Government/None	834 (70)	97.8 (95.3-100.3)	89.1 (86.5-91.8)		0.61 (0.41-0.92)	.02	0.67 (0.49-0.92)	.01
Comorbidity Score								
0	1401 (61)	68.4 (67.7-69.1)	94.6 (93.1-96.2)	<.001	1 [Reference]		1 [Reference]	
1	246 (19)	66.3 (64.2-68.4)	88.5 (83.4-93.9)		0.79 (0.55-1.15)	.23	0.90 (0.70-1.17)	.43
2	50 (12)	52.7 (44.9-60.5)	73.6 (59.7-90.8)		0.24 (0.10-0.57)	.001	0.72 (0.51-1.03)	.07
Prior Cancer								
No	1313 (59)	102.8 (101.3-104.3)	94.2 (92.7-95.8)	<.001	1 [Reference]		1 [Reference]	
Yes	384 (33)	93.1 (86.2-99.9)	89.4 (85.3-93.7)		0.62 (0.43-0.88)	.009	0.93 (0.77-1.13)	.46

Significance determined by Log-Rank test or Wald test. OS: Overall survival; mo: months; HR (95% CI): Hazard ratio (95% confidence interval); P: P-value; N: Number of patients; CTC: Circulating tumor cell; RT: Radiotherapy; LVI: Lymphovascular Invasion; ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2.

eTable 6. Kaplan-Meier Estimates and Multivariable Survival Models for Disease-Free Survival From the SUCCESS Cohort

Variable †	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean DFS (mo) (95% CI)	Five-year DFS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
N (events)					1,516 (153)		1,176 (118)	
Age (per year)					1.01 (0.99-1.03)	.36	1.00 (0.98-1.01)	.85
CTC status and RT								
CTC x RT Interaction Coefficient						**.04**		**.04**
CTC+ RT-	46 (8)	73.7 (62.9-84.4)	75.2 (61.5-91.9)		1 [Reference]		1 [Reference]	
CTC+ RT+	248 (35)	81.1 (78.0-84.2)	88.0 (83.9-92.4)	.002	3.77 (1.77-8.03)	<.001	2.83 (2.02-3.98)	<.001
CTC- RT-	216 (23)	82.0 (78.4-85.7)	88.3 (83.5-93.4)		3.28 (1.51-7.12)	.002	2.16 (1.41-3.33)	<.001
CTC- RT+	1006 (87)	84.9 (83.6-86.3)	92.3 (90.5-94.0)		5.05 (2.47-10.33)	<.001	3.61 (2.58-5.03)	<.001
Grade								
1	77 (4)	87.3 (83.1-91.5)	96.9 (92.8-100.0)	<.001	1 [Reference]		1 [Reference]	
2	686 (45)	86.1 (84.5-87.7)	95.2 (93.4-96.9)		0.81 (0.42-1.57)	.54	1.21 (0.70-2.08)	.50
3	753 (104)	81.0 (79.0-83.0)	85.9 (83.3-88.6)		0.37 (0.19-0.72)	.004	0.58 (0.34-1.00)	.05
Tumor stage								
1	709 (59)	85.1 (83.3-86.9)	93.1 (91.2-95.1)	.02	1 [Reference]		1 [Reference]	
2	807 (94)	83.0 (81.2-84.8)	88.5 (86.1-90.9)		0.67 (0.53-0.86)	.002	0.91 (0.74-1.13)	.40
Nodal stage								
0	638 (56)	85.0 (83.1-86.9)	91.4 (89.1-93.8)	.21	1 [Reference]		1 [Reference]	
1*	878 (97)	83.1 (81.4-84.8)	90.1 (88.0-92.2)		0.58 (0.44-0.77)	<.001	0.50 (0.40-0.62)	<.001
Histology								
IDC	1265 (133)	83.4 (82.0-84.7)	90.3 (88.6-92.1)	.58	1 [Reference]		1 [Reference]	
ILC	140 (11)	84.7 (79.8-89.6)	92.4 (87.8-97.3)		1.07 (0.68-1.68)	.77	1.13 (0.83-1.54)	.44
Other	111 (9)	85.4 (81.6-89.2)	92.0 (86.8-97.5)		1.08 (0.68-1.76)	.73	1.50 (1.02-2.21)	.04
ER status								
Positive	1018 (80)	85.7 (84.3-87.1)	92.8 (91.1-94.5)	<.001	1 [Reference]		1 [Reference]	
Negative	502 (73)	79.8 (77.4-82.2)	86.5 (83.3-89.7)		0.59 (0.37-0.94)	.03	0.60 (0.40-0.89)	.01
PR status								
Positive	963 (80)	85.4 (83.8-87.0)	92.2 (90.4-94.1)	.003	1 [Reference]		1 [Reference]	
Negative	553 (73)	81.3 (79.0-83.6)	88.0 (85.2-90.9)		1.01 (0.68-1.50)	.97	1.57 (1.13-2.18)	.007
ERBB2								
Negative	1151 (124)	83.2 (81.7-84.6)	90.0 (88.2-91.9)	.18	1 [Reference]		1 [Reference]	
Positive	365 (29)	85.4 (83.2-87.7)	92.7 (89.9-95.6)		1.57 (1.16-2.13)	.004	1.43 (1.16-1.77)	<.001
Hormone therapy								
No	438 (59)	79.5 (76.8-82.3)	86.1 (82.6-89.8)	<.001	1 [Reference]		1 [Reference]	
Yes	1078 (94)	85.3 (83.9-86.6)	92.4 (90.7-94.1)		1.16 (0.78-1.74)	.46	1.78 (1.28-2.48)	<.001

Variable †	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean DFS (mo) (95% CI)	Five-year DFS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
Menopausal Status								
Pre-menopausal	676 (61)	85.1 (83.3-86.9)	92.0 (89.9-94.2)	0.21	1 [Reference]		1 [Reference]	
Post-menopausal	840 (92)	83.0 (81.3-84.8)	89.5 (87.3-91.8)		0.79 (0.53-1.17)	.25	1.13 (0.84-1.53)	.42

Significance determined by Log-Rank test or Wald test. DFS (mo): Disease-free survival (months); TR (95% CI): Time ratio (95% confidence interval); P: P-value; CTC: Circulating tumor cell. RT: Radiotherapy; ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2. *includes N1mi (microscopic) and N1. †Association of CTC-status and radiotherapy have been adjusted for type of chemotherapy regimen, but survival estimates associated with chemotherapy have not been listed as the primary trial outcomes of the SUCCESS trial have yet to be published.

eTable 7. Kaplan-Meier Estimates and Multivariable Survival Models for Local Recurrence-Free Survival From the SUCCESS Cohort

Variable †	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean LRFS (mo) (95% CI)	Five-year LRFS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
N (events)					1516 (41)		1176 (31)	
Age (per year)					1.02 (0.99-1.05)	.29	1.03 (1.01-1.05)	.01
CTC status and RT								
CTC x RT Interaction Coefficient						**.13**		**.20**
CTC+ RT-	46 (4)	82.8 (74.1-91.5)	85.7 (73.6-99.8)		1 [Reference]		1 [Reference]	
CTC+ RT+	248 (7)	90.3 (88.8-91.8)	98.2 (96.4-100.0)	.003	3.59 (1.45-8.94)	.005	4.35 (2.60-7.28)	<.001
CTC- RT-	216 (7)	89.8 (88.0-91.6)	96.2 (93.3-99.2)		2.65 (1.11-6.36)	.03	2.12 (1.21-3.72)	.008
CTC- RT+	1006 (23)	90.1 (89.2-91.1)	98.1 (97.3-99.0)		4.31 (1.88-9.86)	<.001	5.99 (3.36-10.70)	<.001
Grade								
1/2	763 (49)	86.5 (84.8-88.1)	95.3 (93.7-97.0)	<.001	1 [Reference]		1 [Reference]	
3	753 (32)	88.2 (86.9-89.6)	96.2 (94.7-97.6)		0.33 (0.18-0.61)	<.001	0.32 (0.21-0.48)	<.001
Tumor stage								
1	709 (17)	90.4 (89.4-91.5)	98.4 (97.4-99.4)	.47	1 [Reference]		1 [Reference]	
2	807 (24)	89.8 (88.7-90.9)	97.0 (95.8-98.3)		0.74 (0.48-1.15)	.18	1.10 (0.78-1.54)	.60
Nodal stage								
0	638 (17)	89.3 (87.9-90.6)	97.8 (96.6-99.0)	.90	1 [Reference]		1 [Reference]	
1*	878 (24)	89.7 (88.8-90.6)	97.5 (96.5-98.6)		0.65 (0.41-1.03)	.07	0.56 (0.40-0.79)	<.001
Histology								
IDC	1266 (35)	90.0 (89.2-90.9)	87.6 (96.7-98.5)	.95	1 [Reference]		1 [Reference]	
ILC	140 (3)	88.4 (83.1-93.7)	98.2 (95.9-100.0)		0.88 (0.39-2.01)	.76	1.52 (0.77-3.01)	.23
Other	110 (3)	90.3 (87.9-92.7)	97.0 (93.8-100.0)		1.05 (0.48-2.34)	.90	1.46 (0.75-2.86)	.26
ER status								
Positive	1015 (23)	90.6 (89.7-91.4)	98.0 (97.1-99.0)	.13	1 [Reference]		1 [Reference]	
Negative	501 (18)	89.0 (87.3-90.7)	96.9 (95.3-98.5)		0.76 (0.37-1.56)	.46	0.46 (0.24-0.87)	.02
PR status								
Positive	963 (23)	90.4 (89.6-91.2)	97.9 (97.0-98.9)	.38	1 [Reference]		1 [Reference]	
Negative	553 (18)	89.1 (87.6-90.6)	97.2 (95.8-98.7)		1.01 (0.52-1.97)	.97	1.40 (0.84-2.35)	.19
ERBB2								
Negative	438 (13)	88.4 (86.3-90.4)	97.3 (95.6-99.0)	.32	1 [Reference]		1 [Reference]	
Positive	1078 (28)	90.0 (89.3-90.8)	97.8 (96.9-98.7)		1.52 (0.86-2.66)	.15	1.43 (1.00-2.05)	.05
Hormone therapy								
No	438 (13)	88.4 (86.3-90.4)	97.3 (95.6-99.0)	.32	1 [Reference]		1 [Reference]	
Yes	1078 (28)	90.0 (89.3-90.8)	97.8 (96.9-98.7)		0.86 (0.43-1.70)	67	0.91 (0.54-1.55)	.74

Variable †	Kaplan Meier Estimates	Accelerated Failure Time Multivariable Analysis

	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean LRFS (mo) (95% CI)	Five-year LRFS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
Menopausal Status								
Pre-menopausal	676 (22)	89.1 (87.8-90.4)	97.7 (96.5-98.9)	.34	1 [Reference]		1 [Reference]	
Post-menopausal	840 (19)	90.0 (89.1-90.9)	97.7 (96.6-98.8)		1.01 (0.52-1.99)	.97	1.16 (0.71-1.89)	.54

Significance determined by Log-Rank test or Wald test. LRFS (mo): Local recurrence-free survival (months); TR (95% CI): Time ratio (95% confidence interval); P: P-value; CTC: Circulating tumor cell. RT: Radiotherapy; ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2. *includes N1mi (microscopic) and N1. †Association of CTC-status and radiotherapy have been adjusted for type of chemotherapy regimen, but survival estimates associated with chemotherapy have not been listed as the primary trial outcomes of the SUCCESS trial have yet to be published.

eTable 8. Kaplan-Meier Estimates and Multivariable Survival Models for Overall Survival From the SUCCESS Cohort

Variable †	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Five-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
N (events)					1,516 (77)		1,176 (67)	
Age (per year)					0.99 (0.97-1.01)	.37	0.99 (0.97-1.00)	.15
CTC status and RT								
CTC x RT Interaction Coefficient						**.16**		**.23**
CTC+ RT-	46 (5)	81.5 (73.2-89.9)	84.5 (72.7-98.2)		1 [Reference]		1 [Reference]	
CTC+ RT+	248 (20)	86.8 (84.8-88.9)	92.4 (88.9-95.9)	.008	2.73 (1.16-6.41)	.02	2.05 (1.41-2.97)	<.001
CTC- RT-	216 (11)	87.4 (84.9-89.9)	95.2 (92.0-98.5)		2.92 (1.22-6.99)	.02	1.99 (1.21-3.30)	.007
CTC- RT+	1006 (41)	88.9 (88.0-89.8)	96.7 (95.6-97.9)		4.04 (1.80-9.08)	<.001	2.89 (1.96-4.25)	<.001
Grade								
1	77 (3)	89.6 (86.9-92.3)	96.9 (92.8-100.0)	<.001	1 [Reference]		1 [Reference]	
2	686 (17)	90.4 (89.7-91.1)	98.0 (96.9-99.1)		1.35 (0.60-3.03)	.46	1.55 (0.87-2.75)	.14
3	753 (17)	86.4 (84.9-87.8)	93.1 (91.2-95.0)		0.58 (0.26-1.30)	.19	0.88 (0.49-1.56)	.65
Tumor stage								
1	709 (23)	90.0 (89.2-90.9)	97.3 (96.0-98.6)	.002	1 [Reference]		1 [Reference]	
2	807 (54)	87.4 (86.1-88.7)	93.9 (92.2-95.7)		0.63 (0.46-0.87)	.005	0.74 (0.58-0.93)	.01
Nodal stage								
0	638 (24)	89.3 (88.2-90.3)	96.4 (84.9-98.0)	.06	1 [Reference]		1 [Reference]	
1*	878 (53)	87.7 (86.5-88.8)	94.9 (93.3-96.4)		0.52 (0.36-0.74)	<.001	0.40 (0.31-0.53)	<.001
Histology								
IDC	1265 (67)	87.9 (87.0-88.7)	95.1 (93.9-96.4)	.62	1 [Reference]		1 [Reference]	
ILC	140 (6)	88.4 (86.0-90.9)	97.5 (94.8-100.0)		0.80 (0.46-1.38)	.42	0.80 (0.58-1.12)	.19
Other	111 (4)	88.5 (85.8-91.2)	97.0 (93.7-100.0)		1.41 (0.73-2.74)	.31	1.70 (1.04-2.78)	.04
ER status								
Positive	1015 (35)	89.5 (88.6-90.3)	97.2 (96.1-98.3)	<.001	1 [Reference]		1 [Reference]	
Negative	501 (42)	86.1 (84.4-87.8)	92.2 (89.7-94.7)		0.73 (0.40-1.32)	.29	0.99 (0.59-1.67)	.96
PR status								
Positive	963 (36)	89.6 (88.6-90.5)	96.7 (95.5-98.0)	.002	1 [Reference]		1 [Reference]	
Negative	553 (41)	87.0 (85.4-88.6)	93.4 (91.2-95.6)		1.23 (0.72-2.12)	.45	1.82 (1.16-2.83)	.008
ERBB2 status								
Negative	1151 (62)	88.5 (87.5-89.4)	95.2 (93.9-96.5)	.42	1 [Reference]		1 [Reference]	
Positive	365 (15)	89.2 (87.7-90.7)	96.5 (94.5-98.5)		1.56 (1.05-2.32)	.03	1.27 (0.99-1.62)	.06
Hormone therapy								
No	438 (59)	79.5 (76.8-82.3)	86.1 (82.6-89.8)	<.001	1 [Reference]		1 [Reference]	
Yes	1078 (94)	85.3 (83.9-86.6)	92.4 (90.7-94.1)		2.13 (1.28-3.53)	.004	4.11 (2.69-6.28)	<.001
Menopausal Status				.04				

Variable †	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Five-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
Pre-menopausal	676 (26)	89.6 (88.5-90.7)	97.1 (95.8-98.5)		1 [Reference]		1 [Reference]	
Post-menopausal	844 (51)	87.9 (86.7-89.1)	94.1 (92.5-95.9)		1.05 (0.64-1.71)	85	1.03 (0.73-1.45)	.88

Significance determined by Log-Rank test or Wald test. OS (mo): Overall survival (months); TR (95% CI): Time ratio (95% confidence interval); P: P-value; N: Number of patients; CTC: Circulating tumor cell. RT: Radiotherapy; ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2 Receptor. *includes N1mi (microscopic) and N1. †Association of CTC-status and radiotherapy have been adjusted for type of chemotherapy regimen, but survival estimates associated with chemotherapy have not been listed as the primary trial outcomes of the SUCCESS trial have yet to be published.

eTable 9. Kaplan-Meier Estimates and Multivariable Survival Models for Overall Survival of Patients Who Underwent Breast-Conserving Surgery From the Pooled Cohort

Variable	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Five-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
N (events)					2,175 (101)		1,840 (87)	
Age (per year)					0.97 (0.95-0.98)	<.001	0.96 (0.95-0.97)	<.001
CTC status and RT								
CTC x RT Interaction Coefficient						**004**		**<.001**
CTC+ RT-	49 (9)	73.6 (63.7-83.5)	73.3 (59.4-90.3)		1 [Reference]		1 [Reference]	
CTC+ RT+	411	87.2 (85.6-88.8)	93.6 (90.8-96.6)	<.001	3.42 (1.47-8.00)	.004	3.42 (2.17-5.40)	<.001
CTC- RT-	163 (8)	86.0 (82.7-89.3)	92.7 (87.3-98.3)		3.10 (1.33-7.24)	.009	2.82 (1.65-4.81)	<.001
CTC- RT+	1554	87.8 (87.0-88.6)	95.5 (94.3-96.6)		3.70 (1.69-8.09)	.001	3.41 (2.21-5.28)	<.001
Grade								
1	324 (15)	87.9 (85.9-89.9)	92.3 (88.4-96.4)	.003	1 [Reference]		1 [Reference]	
2	1018 (30)	89.7 (88.8-90.5)	96.4 (95.1-97.8)		1.41 (0.88-2.25)	.15	1.76 (1.07-2.90)	.03
3	834 (56)	86.9 (85.6-88.2)	92.9 (91.0-94.9)		0.69 (0.41-1.16)	.16	0.73 (0.50-1.06)	.09
Tumor stage								
1	1406 (56)	98.2 (97.1-99.3)	95.1 (93.8-96.5)	.27	1 [Reference]		1 [Reference]	
2	771 (45)	97.0 (95.4-98.6)	93.7 (91.8-95.6)		0.82 (0.60-1.13)	.22	0.96 (0.49-1.86)	.89
Nodal stage								
0	1493 (67)	97.5 (96.2-98.9)	94.0 (92.5-95.5)	.44	1 [Reference]		1 [Reference]	
1*	684 (34)	98.5 (97.1-99.8)	95.3 (93.6-97.0)		0.77 (0.53-1.11)	.16	0.52 (0.26-1.02)	.06
Histology								
IDC	1800 (86)	97.8 (96.7-98.8)	94.5 (93.3-95.7)	.54	1 [Reference]		1 [Reference]	
ILC/Mixed	376 (15)	98.9 (97.1-100.7)	94.5 (91.7-97.3)		1.12 (0.74-1.69)	.59	1.10 (0.28-4.37)	.89
ER status								
Positive	1623 (63)	98.3 (97.4-99.3)	95.2 (93.9-96.4)	.02	1 [Reference]		1 [Reference]	
Negative	554 (38)	95.9 (93.7-98.0)	92.8 (90.5-95.2)		0.66 (0.37-1.20)	.18	0.71 (0.16-3.17)	.65
PR status								
Positive	1483 (62)	98.1 (97.1-99.1)	94.7 (93.3-96.1)	.27	1 [Reference]		1 [Reference]	
Negative	694 (39)	96.8 (94.9-98.6)	94.1 (92.2-96.1)		1.56 (0.92-2.64)	.10	1.78 (0.25-1.26)	.56
ERBB2 status								
Negative	1825 (87)	97.0 (96.0-98.0)	94.3 (93.1-95.6)	.31	1 [Reference]		1 [Reference]	
Positive	352 (14)	98.2 (96.3-100.1)	95.4 (93.0-97.9)		1.37 (0.87-2.14)	.17	1.15 (0.76-1.74)	.50
Chemotherapy								
No	742 (37)	96.8 (94.9-98.6)	91.4 (88.5-94.4)	.005	1 [Reference]		1 [Reference]	
Yes	1435 (64)	98.6 (97.6-99.6)	95.5 (94.4-96.7)		1.43 (0.90-2.26)	.13	1.10 (0.79-1.53)	.56
Variable	**Kaplan Meier Estimates**				**Accelerated Failure Time Multivariable Analysis**			

	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Five-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
Hormone therapy								
No	609 (44)	94.7 (92.3-97.1)	91.4 (88.8-94.0)	<.001	1 [Reference]		1 [Reference]	
Yes	1568 (57)	98.7 (97.8-99.6)	95.7 (94.5-96.9)		1.63 (1.05-2.53)	.31	1.64 (0.35-7.64)	.53

Significance determined by Log-Rank test or Wald test. OS (mo): Overall survival (months); TR (95% CI): Time ratio (95% confidence interval); P: P-value; N: Number of patients; CTC: Circulating tumor cell. RT: Radiotherapy; ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2 Receptor. *includes N1mi (microscopic) and N1.

eTable 10. Kaplan-Meier Estimates and Multivariable Survival Models for Overall Survival of Patients Who Underwent Mastectomy From the Pooled Cohort

Variable	Kaplan Meier Estimates				Accelerated Failure Time Multivariable Analysis			
	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Five-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
N (events)					1,036 (68)		932 (61)	
Age (per year)					0.97 (0.96-0.98)	<.001	0.97 (0.96-0.98)	<.001
CTC status and RT								
CTC x RT Interaction Coefficient						**.82**		**.87**
CTC+ RT-		82.6 (78.7-86.5)	84.3 (76.0-93.6)		1 [Reference]		1 [Reference]	
CTC+ RT+	64 (7)	82.0 (76.1-87.9)	88.3 (79.9-97.6)	.30	0.90 (0.51-1.58)	.36	0.96 (0.70-1.31)	.78
CTC- RT-	616 (37)	84.0 (81.8-86.2)	91.0 (87.8-94.2)		1.34 (0.94-1.92)	.11	1.38 (1.14-1.68)	.001
CTC- RT+	187 (10)	85.1 (82.1-88.1)	95.8 (92.6-99.2)		1.30 (0.80-2.11)	.30	1.66 (1.16-2.37)	.006
Grade								
1	173 (9)	82.2 (73.4-91.0)	88.9 (80.7-97.9)	.36	1 [Reference]		1 [Reference]	
2	503 (29)	86.9 (84.7-89.0)	92.5 (89.6-95.5)		0.91 (0.58-1.41)	.71	0.63 (.49-0.81)	<001
3	360 (30)	83.8 (80.7-86.9)	89.2 (85.2-93.3)		0.74 (0.45-1.20)	.14	0.53 (0.39-0.73)	<.001
Tumor stage								
1	595 (28)	91.1 (87.4-94.8)	92.6 (89.6-95.7)	.09	1 [Reference]		1 [Reference]	
2	441 (40)	87.9 (84.4-91.4)	89.2 (85.8-92.8)		0.72 (0.53-0.98)	.04	1.11 (0.86-1.45)	.40
Nodal stage								
0	755 (45)	90.9 (88.4-93.4)	89.4 (86.0-92.9)	.35	1 [Reference]		1 [Reference]	
1*	281 (23)	89.2 (85.2-93.2)	93.2 (90.0-96.5)		0.70 (0.48-1.02)	.06	0.54 (0.44-0.67)	<.001
Histology								
IDC	815 (51)	88.8 (86.6-91.1)	91.1 (88.5-93.7)	.50	1 [Reference]		1 [Reference]	
ILC/Mixed	221 (17)	81.0 (77.5-84.6)	91.1 (86.3-96.2)		0.98 (0.71-1.34)	.88	0.92 (0.75-1.11)	38
ER status								
Positive	831 (49)	89.4 (85.8-93.1)	91.8 (89.4-94.4)	.14	1 [Reference]		1 [Reference]	
Negative	205 (19)	87.6 (82.7-92.5)	87.9 (82.5-93.6)		1.40 (0.85-2.31)	.19	0.76 (0.45-1.28)	.30
PR status								
Positive	748 (41)	89.5 (85.4-93.6)	92.1 (89.5-94.7)	.04	1 [Reference]		1 [Reference]	
Negative	288 (27)	86.2 (81.4-91.0)	88.5 (84.0-93.2)		0.86 (0.56-1.30)	.47	1.20 (0.91-1.59)	20
ERBB2 status								
Negative	856 (55)	89.2 (86.3-92.2)	90.5 (87.9-93.3)	.87	1 [Reference]		1 [Reference]	
Positive	180 (13)	89.0 (83.7-94.2)	92.7 (88.3-97.2)		0.99 (0.68-1.42)	.94	1.35 (0.74-2.45)	.32
Chemotherapy								
No	438 (34)	79.3 (76.5-82.0)	82.3 (75.4-89.8)	<.001	1 [Reference]		1 [Reference]	
Yes	598 (34)	83.1 (81.7-84.6)	94.1 (91.9-96.4)		1.65 (1.10-2.48)	.02	1.35 (0.88-2.08)	.17
Variable	**Kaplan Meier Estimates**				**Accelerated Failure Time Multivariable Analysis**			

	All patients				All patients		Matched Cohorts	
	N (events)	Restricted Mean OS (mo) (95% CI)	Five-year OS (%) (95% CI)	Log-Rank P	TR (95% CI)	P Value	TR (95% CI)	P Value
Hormone therapy								
No	287 (36)	83.2 (78.2-88.3)	81.1 (75.0-87.6)	<.001	1 [Reference]		1 [Reference]	
Yes	749 (32)	91.2 (87.5-94.8)	94.5 (92.4-96.7)		2.11 (1.44-3.09)	<.001	2.29 (1.77-2.97)	<.001

Significance determined by Log-Rank test or Wald test. OS (mo): Overall survival (months); TR (95% CI): Time ratio (95% confidence interval); P: P-value; N: Number of patients; CTC: Circulating tumor cell. RT: Radiotherapy; ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2 Receptor. *includes N1mi (microscopic) and N1.

eTable 11. Additional Characteristics of the NCDB Cohort Grouped by CTC Status

Variable	CTC-negative (N=1298)	CTC-positive (N=399)	P Value	SMD
LVI				
Negative	988 (76.1)	287 (71.9)	.02	0.15
Positive	95 (7)	47 (12)		
Unknown	215 (16.6)	65 (16)		
Race				
White	998 (76.9)	316 (79.2)	.37	0.06
Black/Other	300 (23.1)	83 (20.8)		
Hispanic				
No	1238 (95.4)	378 (94.7)	.59	0.03
Yes	60 (5)	21 (5)		
Insurance Status				
Private	668 (51.5)	195 (48.9)	.39	0.05
Government/None	630 (48.5)	204 (51.1)		
Comorbidity Score				
0	1055 (81.3)	346 (86.7)	.03	0.16
1	200 (15.4)	46 (12)		
2	43 (3)	7 (2)		
Prior Cancer				
No	1003 (77.3)	310 (77.7)	.89	0.01
Yes	295 (22.7)	89 (22.3)		
Facility Type				
Academic	382 (29.4)	133 (33.3)	.006	0.22
Community Center	120 (9.2)	52 (13)		
Comprehensive	621 (47.8)	182 (45.6)		
Integrated Center	175 (13.5)	32 (8)		
Income quartile				
Top	469 (36.1)	138 (34.6)	.95	0.03
2nd	320 (24.7)	102 (25.6)		
3rd	297 (22.9)	92 (23)		
Bottom	212 (16.3)	67 (17)		
Education quartile				
Top	334 (25.7)	108 (27.1)	.98	0.04
2nd	409 (31.5)	123 (30.8)		
3rd	355 (27.3)	108 (27.1)		
Bottom	200 (15.4)	60 (15)		
Population				
Urban	1148 (88.4)	360 (90.2)	.36	0.06
Nonurban	150 (11.6)	39 (10)		

Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher's exact test or Kruskal-Wallis test. Missing data was coded as "Unknown". P: P-value; SMD: Standardized Mean Difference; CTC: Circulating tumor cell; LVI: Lymphovascular Invasion.

eTable 12. Adjusted Odds Ratios for Factors Associated With CTC-Positive Status of Patients From the NCDB Cohort

Variable	OR (95% CI)	P Value
Age	0.98 (0.97-0.99)	.01
Grade		.28
1	1 [Reference]	
2	0.81 (0.61-1.06)	.01
3	0.80 (0.56-1.15)	.13
Histology		
IDC	1 [Reference]	
ILC/Mixed	1.34 (0.99-1.79)	.05
LVI		.12
Negative	1 [Reference]	
Positive	1.49 (0.99-2.21)	.05
Unknown	0.93 (0.67-1.27)	.64
Tumor stage		
1	1 [Reference]	
2	1.23 (0.93-1.63)	.14
Nodal stage		
0	1 [Reference]	
1 (microscopic)	1.84 (1.14-2.93)	.01
ER status		
Positive	1 [Reference]	
Negative	0.53 (0.32-0.89)	.02
PR status		
Positive	1 [Reference]	
Negative	0.86 (0.59-1.24)	.42
ERBB2 status		.001
Negative	1 [Reference]	
Positive	2.02 (1.38-2.92)	<.001
Race		
White	1 [Reference]	
Black/Other	0.99 (0.72-1.34)	.93
Hispanic Ethnicity		.39
No	1 [Reference]	
Yes	1.02 (0.58-1.74)	.94
Insurance status		.03
Private	1 [Reference]	
Government/None	1.37 (1.03-1.81)	
Comorbidity score		.13
0	1 [Reference]	
1	0.75 (0.52-1.06)	.10
2	0.58 (0.23-1.26)	.20
Prior cancer		
No	1 [Reference]	
Yes	1.04 (0.78-1.38)	.78
Facility Type		.01
Academic	1 [Reference]	
Community Center	1.28 (0.85-1.90)	.23
Comprehensive Center	0.85 (0.64-1.12)	.24
Integrated Center	0.53 (0.33-0.81)	.004
Educational quartile		.70
Top	1 [Reference]	
2nd	0.89 (0.63-1.24)	.48
3rd	0.84 (0.55-1.26)	.39
Bottom	0.74 (0.45-1.21)	.24
Income quartile		.54

Variable	OR (95% CI)	P Value
Bottom	1 [Reference]	
3rd	0.90 (0.61-1.34)	.61
2nd	0.84 (0.55-1.28)	.42
Top	0.68 (0.42-1.09)	11
Region		
Urban	1 [Reference]	
Non-urban	0.71 (0.47-1.05)	.09

Significance determined by Likelihood Ratio Test with p-values calculated using the χ^2 distribution. OR (95% CI): Odds ratio (95% confidence interval); P: P-value; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; LVI: Lymphovascular Invasion; ER: Estrogen Receptor; ER: Estrogen Receptor; *ERBB2*: Human epidermal receptor growth factor 2 Receptor.

eTable 13. Characteristics of the Merged Cohorts Grouped by Receipt of Radiation

Variable	No Radiation (N=997)	Radiation (N=2216)	P Value	SMD
Age (year)	60.0 [50.0, 70.0]	56.0 [48.0, 65.0]	<.001	0.32
CTC				
CTC+	218 (21.9)	475 (21.4)	.78	0.01
CTC-	779 (78.1)	1741 (78.6)		
Tumor stage				
1	649 (65.1)	1352 (61.0)	.03	0.09
2	348 (34.9)	864 (39.0)		
Nodal stage				
0	808 (81.0)	1440 (65.0)	<.001	0.37
1*	189 (19.0)	776 (35.0)		
Grade				
1	195 (19.6)	302 (13.6)	<.001	0.18
2	475 (47.6)	1046 (47.2)		
3	327 (32.8)	867 (39.1)		
Histology				
IDC	792 (79.4)	1823 (82.3)	.06	0.07
ILC/Mixed	205 (20.6)	392 (17.7)		
ER status				
Positive	804 (80.6)	1650 (74.5)	<.001	0.15
Negative	193 (19.4)	566 (25.5)		
PR status				
Positive	728 (73.0)	1503 (67.8)	.003	0.11
Negative	269 (27.0)	713 (32.2)		
ERBB2 status				
Negative	849 (85.2)	1832 (82.7)	.08	0.07
Positive	148 (14.8)	384 (17.3)		
Surgery				
BCS	212 (21.3)	1965 (88.7)	<.001	1.84
Mastectomy	785 (78.7)	251 (11.3)		
Radiation Volumes				
None	997 (100.0)	0 (0)		
Breast	0 (0)	2116 (95.5)	<.001	4.46
Breast and LN	0 (0)	65 (3)		
Not reported	0 (0)	35 (2)		

Data are presented as count (percentage) or median (interquartile range), with significance determined by Fisher's exact test or Kruskal-Wallis test. P: P-value; SMD: Standardized Mean Difference; Follow-up (mo): Follow-up (months); CTC: Circulating tumor cell; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma, ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2 Receptor; BCS: Breast-conserving surgery; Mast: Mastectomy. *includes N1mi (microscopic) and N1.

eTable 14. Characteristics of the Patients Within the Merged Cohorts Who Received Breast-Conserving Surgery or Mastectomy Grouped by Receipt of Radiation

Variable	Breast-conserving surgery				Mastectomy			
	No Radiation (N=212)	Radiation (N=1,965)	P Value	SMD	No Radiation (N=785)	Radiation (N=251)	P Value	SMD
Age (year)	65.5 [53.8, 74.3]	57.0 [48.0, 65.0]	<.001	0.55	59.0 [50.0, 68.0]	51.0 [45.0, 60.0]	<.001	0.57
CTC status								
CTC+	49 (23)	411 (20.9)	.48	0.05	169 (21.5)	64 (25.5)	.19	0.09
CTC-	163 (76.9)	1554 (79.1)			616 (78.5)	187 (74.5)		
Tumor stage								
1	149 (70.3)	1257 (64.0)	.08	0.14	500 (63.7)	95 (37.8)	<.001	0.54
2	63 (30)	708 (36.0)			285 (36.3)	156 (62.2)		
Nodal stage								
0	169 (79.7)	1324 (67.4)	<.001	0.28	639 (81.4)	116 (46.2)	<001	0.79
1*	43 (20)	641 (32.6)			114 (14.5)	130 (51.8)		
Grade								
1	40 (19)	284 (14.5)	.14	0.14	155 (19.7)	18 (7)	<.001	0.38
2	101 (47.6)	917 (46.7)			374 (47.6)	129 (51.4)		
3	71 (34)	763 (38.8)			256 (32.6)	104 (41.4)		
Histology								
IDC	173 (81.6)	1627 (82.8)	.63	0.03	619 (78.9)	196 (78.1)	.79	0.02
ILC/Mixed	39 (18)	337 (17.2)			166 (21.1)	55 (22)		
ER status								
Positive	167 (78.8)	1456 (74.1)	.16	0.11	637 (81.1)	194 (77.3)	.20	0.10
Negative	45 (21)	509 (25.9)			148 (18.9)	57 (23)		
PR status								
Positive	156 (73.6)	1327 (67.5)	.08	0.13	572 (72.9)	176 (70.1)	.42	0.06
Negative	56 (26)	636 (32.4)			213 (27.1)	75 (30)		
ERBB2 status								
Negative	181 (85.4)	1644 (83.7)	.56	0.05	668 (85.1)	188 (74.9)	<.001	0.26
Positive	31 (15)	321 (16.3)			117 (14.9)	63 (25)		

Data are presented as count (percentage) or median (interquartile range), with significance determined by Fisher's exact test or Kruskal-Wallis test. P: P-value; SMD: Standardized Mean Difference; Follow-up (mo): Follow-up (months); CTC: Circulating tumor cell; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma, ER: Estrogen Receptor; PR: Progesterone Receptor; *ERBB2*: Human epidermal receptor growth factor 2 Receptor.
*includes N1mi (microscopic) and N1.

eTable 15. Sensitivity Analyses for Possible Unmeasured Confounding

TR confounder	Prevalence in treated	Prevalence in control	TR treated	Lower 95% CI	Upper 95% CI
NCDB: CTC+RT+ vs, CTC+RT- (reference); Overall Survival					
2.00	0.7	0.4	1.67	1.27	2.18
3.00	0.7	0.4	1.49	1.13	1.95
4.00	0.7	0.4	1.38	1.05	1.81
5.00	0.7	0.4	1.31	0.99	1.71
2.00	0.6	0.3	1.65	1.26	2.16
3.00	0.6	0.3	1.46	1.11	1.92
4.00	0.6	0.3	1.35	1.02	1.76
5.00	0.6	0.3	1.26	0.96	1.65
TR confounder	**Prevalence in**	**Prevalence in**	**TR treated**	**Lower 95% CI**	**Upper 95% CI**
SUCCESS: CTC+RT+ vs, CTC+RT- (reference) (reference); Disease-Free Survival					
2.00	0.9	0.4	2.18	1.60	2.98
3.00	0.9	0.4	1.84	1.35	2.51
4.00	0.9	0.4	1.65	1.21	2.24
5.00	0.9	0.4	1.52	1.11	2.07
6.00	0.9	0.4	1.42	1.04	1.94
7.00	0.9	0.4	1.35	0.99	1.84
2.00	0.8	0.3	2.16	1.58	2.95
3.00	0.8	0.3	1.79	1.31	2.44
5.00	0.8	0.3	1.44	1.05	1.96
6.00	0.8	0.3	1.34	0.98	1.82

TR: Time Ratio; 95% CI: 95% confidence interval; CTC: Circulating tumor cell; RT: Radiotherapy.