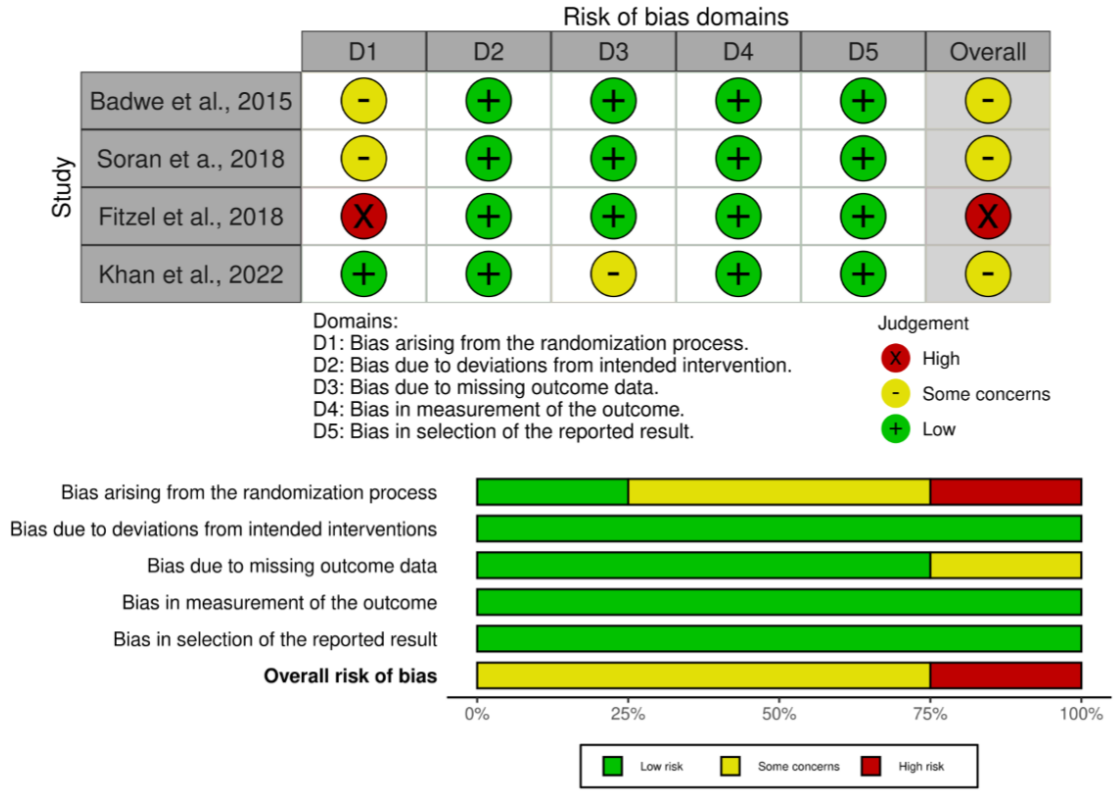

Supplementary Figure 1. RoB 2.0 for RCTs [29-31, 74].

Supplementary Table 1. Keywords and search terms.

Databases	Keywords and search terms for different databases
PubMed	(("Primary resection"[All Fields] OR "Resection"[All Fields] OR "Primary surgery"[All Fields] OR "surgery"[All Fields]) AND ("Stage IV"[All Fields] OR "Stage 4"[All Fields] OR "Metastatic"[All Fields]) AND ("Breast cancer"[All Fields] OR "Breast neoplasms"[All Fields] OR "Breast carcinoma"[All Fields]))
ScienceDirect	(“Primary resection” OR “Primary surgery”) AND (“Stage IV” OR “Stage 4” OR “Metastatic”) AND (“Breast cancer” OR “Breast neoplasms” OR “Breast carcinoma”)
The Cochrane library	((“Primary resection” OR “Resection” OR “Primary surgery” OR “surgery”) AND (“Stage IV” OR “Stage 4” OR “Metastatic”) AND (“Breast cancer” OR “Breast neoplasms” OR “Breast carcinoma”)):ti,ab,kw
Google Scholar and Scopus	(“Primary resection” OR “Resection” OR “Primary surgery” OR “surgery”) AND (“Stage IV” OR “Stage 4” OR “Metastatic”) AND (“Breast cancer” OR “Breast neoplasms” OR “Breast carcinoma”)

Supplementary Table 2. General characteristics of the studies (PTR group).

					HER2 status (%)		Grade (%)		Visceral metastases		PR Status (%)		ER Status (%)		Metastatic site (%)		Bone only metastases (%)	
Study ID	**country**	**N**	**PTR**	**mean age**	**+**	**-**	**G1-2**	**G3**	**Yes**	**No**	**+**	**-**	**+**	**-**	**1**	**>1**	**Yes**	**No**
Observational studies																		
Rapiti et al., 2006[33]	Switzerland	300	127	62	NA	NA	NA	NA	43	47	NA	NA	NA	NA	61	NA	NA	NA
Babiera et al., 2006[34]	USA	224	82	50	37	45	NA	NA	NA	NA	39	45	51	323	82	19	NA	NA
Blanchard et al., 2008[36]	USA	395	242	63	NA	NA	NA	NA	39	61	52	48	82	18	81	19	77	23
Fields et al., 2007[35]	USA	409	187	57	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	24	76
Cady et al., 2008[37]	USA	622	234	60	NA	NA	NA	NA	36	64	NA	NA	61	39	NA	NA	57	43
Hazard et al., 2008[38]	USA	111	47	53	32	68	NA	NA	57	43	NA	NA	NA	NA	74	26	43	57
Shien et al., 2009[42]	Japan	344	160	54	NA	NA	NA	NA	33	67	NA	NA	NA	NA	NA	NA	60	40
Ruiterkamp et al., 2009[41]	Netherland	728	288	60	NA	NA	NA	NA	53	42	NA	NA	NA	NA	21	74	NA	NA

McGuire et al., 2009[40]	USA	566	154	60	5.60	94	NA	NA	57	43	33	67	40	60	NA	NA	43	57
Leung et al., 2010[43]	USA	157	52	54	NA	NA	NA	NA	67	33	NA	NA	NA	NA	NA	NA	33	67
Neuman et al., 2010[44]	USA	186	69	53	17	83	NA	NA	52	48	46	54	70	30	NA	NA	62	38
Ahn et al., 2010[39]	S.Korea	198	110	54	64	36	NA	NA	61	39	50	49	58	41	60	40	34	NA
Pathy et al., 2011[45]	Malaysia	375	139	49	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	47	43.70
Dominici et al., 2011[72]	USA	290	54	53	35	65	NA	NA	NA	NA	NA	NA	72	28	69	31	63	37
Pérez-Fidalgo et al., 2011[46]	Spain	208	123	56	46	54	63	36	42	58	47	53	54	46	69	31	36	64.50
Lang et al., 2013[48]	USA	208	74	-	36	64	NA	NA	NA	NA	28	72	59	41	81	19	35	74.90
Anula et al., 2015[50]	Spain	69	36	55	16	84	50	50	47	53	45	55	NA	NA	69	31	33	67
Rhu et al., 2015[51]	S.Korea	262	40	44	21	79	NA	NA	37	62	65	35	69	31	NA	NA	53	47
Quinn et al., 2015[52]	Ireland	110	52	-	4	96	48	52	56	44	NA	NA	NA	NA	NA	75	51	49
Kolben et al., 2016[54]	Germany	236	196	58	13	45	45	55	20	80	NA	NA	NA	NA	64	36	43	47
Wang et al., 2016[73]	China	157	66	55	45	55	84	17	NA	NA	45	55	46	44	52	48	46	55

Muzaffar et al., 2016[56]	USA	439	222	66	NA	NA	38	51	NA	NA	57	27	72	12	NA	NA	NA	NA
Yoo et al., 2017[57]	S.Korea	2,232	1541	50	21	41	37	34	NA	NA	35	45	47	34	NA	NA	NA	NA
Barinoff et al., 2017[58]	Germany	568	426	59	76	24	NA	NA	77	23	NA	NA	NA	NA	NA	20	57	43
choi et al., 2017[59]	S.Korea	245	82	45	33	65	NA	NA	2	98	43	55	70	28	NA	NA	60	40
Desille-Gbaguidi et al., 2018[60]	France	139	69	56	22	78	NA	NA	44	56	81	19	81	19	70	30	51	49
Lim et al., 2018[61]	S.Korea	284	92	50.8	9	72	34	45	NA	NA	36	61	58	39	82	15	41	69
Wang et al., 2019[63]	China	8142	1891	-	28	69	38	55	NA	NA	54	42	68	29	NA	NA	58	42
Lopez-Tarruella et al., 2019[62]	Spain	1331	592	-	5	17	33	23	40	60	NA	NA	NA	NA	57	30	39	61
Lane et al., 2019[15]	USA	24015	4552	60	NA	NA	NA	NA	NA	NA	58	31	70	20	NA	NA	NA	NA
Si et al., 2020[65]	China	177	77	45	49	37	NA	NA	40	48	54	35	42	46	49	24	40	47
Mudgway et al., 2020[64]	USA	3231	1130	56	NA	NA	NA	NA	67	33	37	34	35	35	NA	NA	41	59.10
Yao et al., 2020[66]	China	7669	2704	-	26	66	NA	NA	NA	NA	54	43	68	29	NA	NA	41	59.10
Bilani et al., 2020[67]	USA	64810	15661	59	16	52	85	6	NA	NA	NA	NA	NA	NA	63	18	56	42.70

Çöpelci et al., 2021[69]	Turkey	117	55	50	12	35	NA	NA	14	85	NA	NA	NA	NA	NA	NA	NA	NA
Huang et al., 2021[70]	China	243	125	50	51	46	NA	NA	51	49	59	41	70	30	NA	NA	55	54.80
Xie et al., 2022[71]	China	13618	4112	58	26	70	NA	NA	58	44	70	30	NA	NA	64	18	41	59.20
RCTs																		
Soran et al., 2018[31]	Turkey	274	138	52	30	70	44	56	NA	NA	NA	NA	NA	NA	NA	NA	51	49
Badwe et al., 2015[29]	India	350	173	48	26	72	NA	NA	NA	NA	59	41	NA	NA	25	75	29	71
Fitzal et al., 2019[30]	Austria	90	45	-	NA	NA	NA	NA	60	40	NA	NA	NA	NA	NA	NA	49	51
Khan et al., 2022[74]	USA	390	125	55	31.7	60.8	NA	NA	10.7	NA	NA	NA	NA	NA	2.5	36.4	38.8	NA

Abbreviations: PTR=Primary Tumor Resection; HER-2= Human epidermal growth factor receptor 2; PR=Progesterone Receptor; ER=Estrogen Receptor ; N0-4=Cancer staging; T1-4=Tumor size; RCT=Randomized Control Trial

1 **Supplementary Table 3. General characteristics of the studies (non-PTR group).**

					HER2 status (%)		Grade (%)		Visceral metastases (%)		PR Status (%)		ER Status (%)		Metastatic site (%)		Bone only metastases (%)	
Study ID	**Country**	**Total N**	**N**	**Mean age**	**+**	**-**	**G1-2**	**G3**	**Yes**	**No**	**+**	**-**	**+**	**-**	**1**	**>1**	**Yes**	**No**
Observational studies																		
Rapiti et al., 2006[33]	Switzerland	300	173	72	NA	NA	NA	NA	58	42	NA	NA	NA	NA	41	NA	NA	NA
Babiera et al., 2006[34]	USA	224	142	55	20	62	NA	NA	NA	NA	51	44	67	30	70	30	NA	NA
Blanchard et al., 2008[36]	USA	395	153	57	NA	NA	NA	NA	67	33	39	61	72	28	49	51	80	20
Fields et al., 2007[35]	USA	409	222	57	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	26	74
Cady et al., 2008[37]	USA	622	388	60	NA	NA	NA	NA	36	64	NA	NA	68	32	NA	NA	57	43
Hazard et al., 2008[38]	USA	111	64	57	27	73	NA	NA	66	34	NA	NA	NA	NA	53	47	34	66
Shien et al., 2009[42]	Japan	344	184	54	NA	NA	NA	NA	67	33	NA	NA	NA	NA	NA	NA	40	60
Ruiterkamp et al., 2009[41]	Netherland	728	440	65	NA	NA	NA	NA	60	34	NA	NA	NA	NA	57	37	NA	NA
McGuire et al., 2009[40]	USA	566	412	52	7	93	NA	NA	65	35	26	74	33	67	NA	NA	35	65
Leung et al., 2010[43]	USA	157	105	60	NA	NA	NA	NA	61	39	NA	NA	NA	NA	NA	NA	39	61
Neuman et al., 2010[44]	USA	186	117	58	41	49	NA	NA	64	36	36	64	68	32	NA	NA	68	32
Ahn et al., 2010[39]	S.Korea	198	88	<50 and >50	70	30	NA	NA	64	36	43	57	61	39	57	43	27	NA
Pathy et al., 2011[45]	Malaysia	375	236	50	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	36	54.40
Dominici et al., 2011[72]	USA	290	236	52	32	68	NA	NA	NA	NA	NA	NA	75	25	64	36	67	33

Pérez-Fidalgo et al., 2011[46]	Spain	208	85	59	61	38	77	23	66	34	52	48	62	38	46	44	14	83.90
Lang et al., 2013[48]	USA	208	134	-	25	74	NA	NA	NA	NA	52	48	68	32	70	30	47	53
Akay et al., 2014[49]	USA	172	93	53	19	75	27	67	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Anula et al., 2015[50]	Spain	69	33	60	17	83	52	48	24	76	46	54	NA	NA	49	51	33	67
Rhu et al., 2015[51]	S.Korea	262	222	49	31	69	NA	NA	32	68	52	48	59	61	NA	NA	63	37
Quinn et al., 2015[52]	Ireland	110	57	-	9	91	67	31	65	34	NA	NA	NA	NA	NA	96	84	16
Kolben et al., 2016[54]	Germany	236	40	57	10	52	75	25	15	85	NA	NA	NA	NA	35	65	20	80
Wang et al., 2016[73]	China	157	91	57	64	37	70	30	NA	NA	54	46	50	50	34	66	51	50
Muzaffar et al., 2016[56]	USA	439	217	65	NA	NA	29	29	NA	NA	45	20	58	10	NA	NA	NA	NA
Yoo et al., 2017[57]	S.Korea	2,232	588	51	12	19	9	7	NA	NA	22	30	29	23	NA	NA	NA	NA
Xie et al., 2017[55]	China	233	46	-	26	61	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Barinoff et al., 2017[58]	Germany	568	142	57	69	31	NA	NA	77	23	NA	NA	NA	NA	NA	39	60	40
Choi et al., 2017[59]	S.Korea	245	163	45	37	61	NA	NA	2	98	53	46	62	37	NA	NA	72	28
Desille-Gbaguidi et al., 2018[60]	France	139	70	68	19	81	NA	NA	71	29	50	50	74	26	43	57	71	29
Lim et al., 2018[61]	S.Korea	284	192	51	34	59	6	5	NA	NA	44	50	60	33	44	56	26	75
Wang et al., 2019[63]	China	8142	6251	-	23	66	42	33	NA	NA	62	32	77	17	NA	NA	75	25
Lopez-Tarruella et al., 2019[62]	Spain	1331	739	-	3	6	11	8	54	46	NA	NA	NA	NA	43	49	30	69
Lane et al., 2019[15]	USA	24015	13505	59	NA	NA	NA	NA	NA	NA	57	31	72	17	NA	NA	NA	NA
Si et al., 2020[65]	China	177	100	<45 >45	51	63	NA	NA	60	52	46	65	59	54	51	76	60	53
Mudgway et al., 2020[64]	USA	3231	2101	59	NA	NA	NA	NA	33	67	63	66	65	65	NA	NA	59	40

Yao et al., 2020[66]	China	7669	4965	-	22	64	NA	NA	NA	NA	58	35	73	21	NA	NA	37.30	63
Bilani et al., 2020[67]	USA	64810	49149	63	13	51	62	6	NA	NA	NA	NA	NA	NA	54	36	69	29
Çöpelci et al., 2021[69]	Turkey	117	62	60	15	38	NA	NA	8	91	NA	NA	NA	NA	NA	NA	NA	NA
Huang et al., 2021[70]	China	243	118	50	45	47	NA	NA	71	29	57	43	64	36	NA	NA	56	54
Xie et al., 2022[71]	China	13618	9020	62	25	71	NA	NA	62	38	77	23	NA	NA	8	39	37	63
RCTs																		
Badwe et al., 2015[29]	India	350	-	48	35	61	NA	NA	NA	NA	60	40	NA	NA	26	74	28	72
Fitzal et al., 2018[30]	Austria	90	45	-	NA	NA	NA	NA	64	36	NA	NA	NA	NA	NA	NA	36	64
Soran et al., 2018[31]	Turkey	274	136	51	31	69	41	59	NA	NA	NA	NA	NA	NA	NA	NA	40	60
Khan et al., 2022[74]	USA	390	131	56	32.8	58.4	NA	NA	11.1	NA	NA	NA	NA	NA	3.2	31.8	44.4	NA

Abbreviations: PTR=Primary Tumor Resection; HER-2= Human epidermal growth factor receptor 2; PR=Progesterone Receptor; ER=Estrogen Receptor; N0-4=Cancer staging; T1-4=Tumor size; RCT=Randomized Control Trial

Supplementary Table 4. NOS table for observational studies quality assessment.

Study ID	Selection	Comparability	Exposure/Outcome	Overall star rating
Khan et al., 2002[32]	++	+	++	5
Rapiti et al., 2006[33]	+++	++	+++	8
Babiera et al., 2006[34]	+++	++	+++	8
Fields et al., 2007[35]	+++	++	+++	8
Blanchard et al., 2008[36]	+++	++	+++	8
Cady et al., 2008[37]	+++	++	+++	8
Hazard et al., 2008[38]	+++	++	+++	8
Shien et al., 2009[42]	+++	++	++	7
Ruiterkamp et al., 2009[41]	+++	++	+++	8
McGuire et al., 2009[40]	+++	++	+++	8
Leung et al., 2010[43]	+++	++	+++	8
Neuman et al., 2010[44]	++	++	+++	7
Ahn et al., 2010[39]	+++	++	+++	8
Pathy et al., 2011[45]	+++	++	+++	8
Dominici et al., 2011[72]	+++	++	+++	8
Pérez-Fidalgo et al., 2011[46]	+++	++	++++	9
Rashaan et al., 2012[47]	+++	+	+++	7
Lang et al., 2013[48]	+++	++	++++	9
Akay et al., 2014[49]	+++	++	+++	8
Anula et al., 2015[50]	++	++	++++	8
Rhu et al., 2015[51]	+++	++	++++	9
Quinn et al., 2015[52]	+++	++	+++	8
Thomas et al., 2016[53]	+++	++	++++	9
Wang et al., 2016[73]	+++	++	++++	9
Kolben et al., 2016[54]	+++	++	+++	8
Muzaffar et al., 2016[56]	+++	++	++++	9
Yoo et al., 2017[57]	++	++	++++	8

Xie et al., 2017[55]	++	++	++++	8
Barinoff et al., 2017[58]	++	++	++++	8
Choi et al., 2017[59]	+++	++	++++	9
Desille-Gbaguidi et al., 2018[60]	+++	++	+++	8
Lim et al., 2018[61]	++	++	++++	8
Wang et al., 2019[63]	+++	++	++++	9
Lopez-Tarruella et al., 2019[62]	+++	++	++++	9
Lane et al., 2019[15]	+++	++	++	7
Si et al., 2020[65]	+++	++	++++	9
Mudgway et al., 2020[64]	+++	++	++++	9
Yao et al., 2020[66]	++	++	++++	8
Bilani et al., 2020[67]	++	++	++++	8
Bilani et al., 2021[68]	++	++	+++	7
Çöpelci et al., 2021[69]	+++	++	+++	8
Huang et al., 2021[70]	+++	++	++++	9
Xie et al., 2022[71]	+++	++	++++	9

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