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ORIGINAL ARTICLE – BREAST ONCOLOGY

Does Breast-Conserving Surgery with Radiotherapy have a Better Survival than Mastectomy? A Meta-Analysis of More than 1,500,000 Patients

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ABSTRACT

Background. There have been conflicting studies reporting on survival advantages between breast-conserving surgery with radiotherapy (BCS) in comparison with mastectomy. Our aim was to compare the efficacy of BCS and mastectomy in terms of overall survival (OS) comparing all past published studies.

Methods. We performed a comprehensive review of literature through October 2021 in PubMed, Scopus, and EMBASE. The studies included were randomized controlled trials (RCTs) and cohorts that compare BCS versus mastectomy. We excluded studies that included male sex, stage 0, distant metastasis at diagnosis, bilateral synchronous cancer, neoadjuvant radiation/chemotherapy, and articles with incomplete data. We performed a meta-analysis following the random-effect model with the inverse variance method.

Results. From 18,997 publications, a total of 30 studies were included in the final analysis: 6 studies were randomized trials, and 24 were retrospective cohorts. A total of 1,802,128 patients with a follow-up ranging from 4 to 20 years were included, and 1,075,563 and 744,565 underwent BCS and mastectomy, respectively. Among the population, BCS is associated with improved OS compared with mastectomy [relative risk (RR) 0.64, 95% confidence interval (CI) 0.55–0.74]. This effect was similar when analysis was performed in cohorts and multi-institutional databases (RR 0.57, 95% CI 0.49–0.67). Furthermore, the benefit of BCS was stronger in patients who had less than 10 years of follow-up (RR 0.54, 95% CI 0.46–0.64).

Conclusions. Patients who underwent BCS had better OS compared with mastectomy. Such results depicting survival advantage, especially using such a large sample of patients, may need to be included in the shared surgical decision making when discussing breast cancer treatment with patients.

There are many clinical and nonclinical factors influencing the choice of breast-conserving surgery with radiotherapy (BCS) versus mastectomy in patients with early-stage invasive breast cancer, including tumor size, tumor stage, age, extent of surgery, radiation, body image, and quality of life.[1, 2] One of the most important principals of shared decision making when comparing BCS and mastectomy is overall survival.

During the past decade, several studies have reported better oncologic outcomes in patients with early-stage invasive breast cancer who had BCS in comparison with mastectomy,[3–15] a concept that contradicts the previous knowledge of similar overall survival between the two groups.[16–22] Many of these previous studies were

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conducted using patient populations in specific regions and include different follow-up times. While the more recent studies have suggested a survival benefit for BCS, there has yet to be a widespread meta-analysis assessing study results from patient populations across the world over the past 20 years. Our aim with this meta-analysis of over 1.8 million patients was to compare the efficacy of BCS and mastectomy in terms of overall survival (OS) in early-stage invasive breast cancer with all the literature available to date around the world.

MATERIALS AND METHODS

This systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and the Cochrane Handbook for Systematic Reviews of Interventions.

Search Strategy

We searched evidence up to 31 October 2021 in the following databases: PubMed, Scopus, and EMBASE. The search strategy can be found in Supplementary Material 1. We did not limit the search by publication date or language.

Inclusion and Exclusion Criteria

We intended to include any trial or cohort studies that compared BCS and mastectomy in patients with breast cancer with American Joint Committee on Cancer (AJCC) stages I–III. We excluded case reports, case series, reviews, letters to the editor, congress or conference abstracts, editorials, interviews, comments, and newspaper articles. We excluded studies that included male sex, stage 0, distant metastasis at diagnosis, bilateral synchronous cancer, neoadjuvant radiation, or chemotherapy in more than 5% of the studied population, oncoplastic surgery, and articles without available hazard ratio (HR) or incomplete data. Moreover, we excluded randomized trials that did not include radiotherapy as an adjunctive treatment with breast conservation surgery;[23–25] studies that had similar databases or had the same years of the study population;[26–37] studies without a hazard ratio, number of population, mortality rate, or overall survival rate available; populations with BRCA1/2 mutation; and populations with neoadjuvant chemotherapy or radiotherapy.

Study Selection

One author (G.D.K.) downloaded all references to an EndNote document to eliminate duplicates. Then, the author exported those references to the Rayyan QCRI webpage (https://rayyan.qcri.org/). Four reviewers (G.A.D.K., A.N., D.P., and S.M.) independently screened titles and abstracts. Those reviewers assessed the full-text version of selected articles to determine eligibility. This selection was performed using a prepiloted Microsoft Excel sheet. Any disagreement was resolved by consensus.

Data Extraction

Two reviewers independently extracted data of interest (G.A.D.K., D.C.M.). For dichotomous outcomes, we extracted absolute and relative frequencies. For continuous outcomes, we extracted baseline and follow-up measurements, as well as the change between them. The extraction was performed using a prepiloted Microsoft Excel sheet.

Primary Outcomes

Overall survival (OS) was the primary outcome when comparing BCS versus mastectomy.

Heterogeneity

The between-study heterogeneity variance was estimated at $\tau^2 = 0.15$ (95% CI 0.09–0.28), with an I^2 value of 98.2% (95% CI 97.9–98.5%), $p < 0.01$. The heterogeneity of the study was high, as shown by the I^2 statistic. Cochran's Q test shows a $p < 0.01$ heterogeneity, which alone is a poor analysis as it is strongly affected by the number of studies or sample size. The prediction interval can overcome I^2 and provides further insight into how BCS, when compared with mastectomy, may be beneficial on the basis of current evidence.[38] The prediction interval ranged from $g = 0.28$ to 1.43, which indicates that a negative intervention effect can likely be ruled out in future studies when comparing BCS with mastectomy.

To assess heterogeneity, we ran influence diagnostics for our primary aim, reviewed the overall pooled cohort, and assessed influential cases or outliers. A Baujat plot visually depicted each studies' contribution to heterogeneity. In Fig. 1, all studies were included, and two articles, de Boniface et al. (2021)[7] and Landescasper (2019),[4] were found to likely be influential in the overall model. Once omitted, Fig. 2 represents our study population overall.

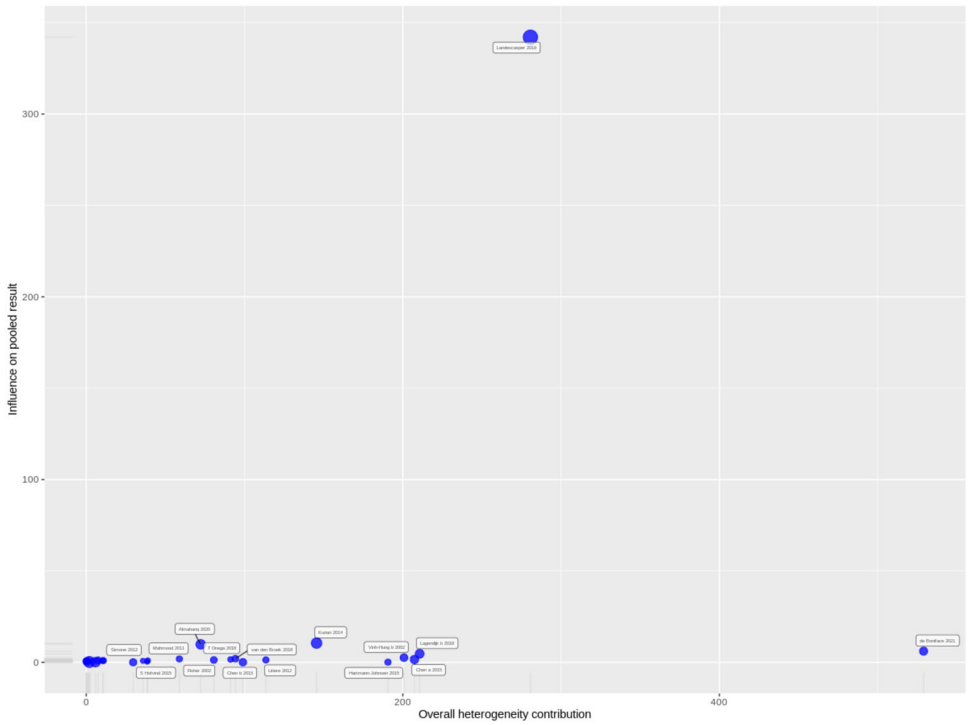

FIG. 1 Baujat plot of all the studies and their contribution to heterogeneity

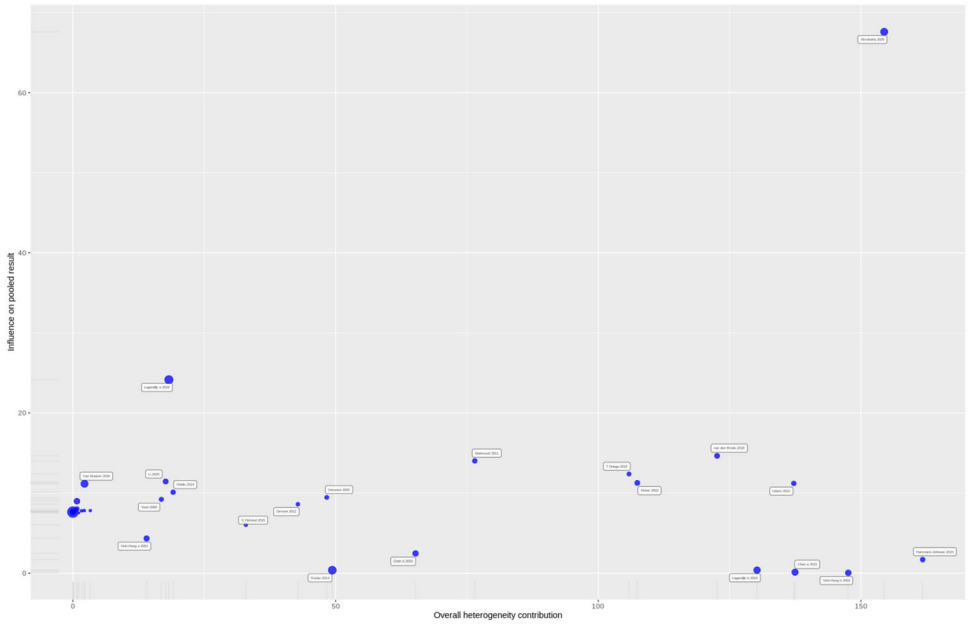

FIG. 2 Baujat plot of all the studies without the most influential studies in the heterogeneity of the overall model[4,7]

Risk of Bias

To account for bias, linear regression of funnel plot asymmetry using Peters' method was used.[39] Here, the regression test assessed the overall cohort accounting for sample size distribution and whether this was skewed. The test was not significant ($t = 0.70$, $p = 0.49$), indicating no funnel plot asymmetry.

In addition to this, we used version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[40] This tool has five domains (randomization process, deviations from intended interventions, missing outcome data, measure-

ment of the outcome, and selection of the reported results) and the overall score. Each domain can be judged as follows: low risk of bias, some concerns, and high risk of bias.

We used the Newcastle–Ottawa scale (NOS) to assess the risk of bias.[41] The NOS assesses three domains: (1) selection of the study groups, (2) comparability of groups, and (3) exposure or outcome according to the study design. We gave one point for each item (two points for a comparability item) according to methodological adequacy. The NOS gives a maximum score of 9 points. Any disagreement was discussed and resolved by consensus.

Data Synthesis

Meta-analyses were performed using a random-effect model with the inverse variance method. We used the Paule–Mandel estimator and Hartung–Knapp–Sidik–Jonkman method for τ^2 and 95% confidence interval (95% CI) calculation, respectively. For dichotomous outcomes, we used relative risks (RRs) with their 95% CIs. We conducted the analyses using functions of the meta library of R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

Selection

We identified 18,997 publications. After removing duplicates and screening phase, we selected 86 articles for full-text screening. Finally, 24 cohort studies[2–16, 42–50] and 6 RCTs[17, 19–21, 51–53] were included in this systematic review (Fig. 3).

Characteristics of Studied Subjects

From a total of 1,802,128 patients, 1,075,563 (58.7%) and 744,565 (41.3%) underwent BCS and mastectomy, respectively. Eleven studies (36.7%) had a follow-up of more than 10 years. Overall survival was the main outcome in 90% of the studies. From all the cohorts, 87.5% were from databases that included patients with breast cancer diagnosis after 2000, while this was present in none of the RCTs. A total of 46.7% of the studies were from Europe, with three of them from Germany (10%); followed by 40% from North America, all of which were from the USA; 10 % from Asia; and 3.3% from South America. Four cohorts also included patients who underwent mastectomy with radiotherapy. In addition, two cohorts and one RCT also assessed patients who underwent conserving surgery without radiotherapy (Table 1).

The sample size from the studies ranged from 237 to 845,136 patients in cohorts, and 179 to 1217 patients in RCTs. All the patients were female, the mean/median age ranged from 43 to 68 (IQR) years, and from 43 (IQR 57–61) to 66 (IQR 59–61) years for BCS and mastectomy, respectively. The median follow-up ranged from 4 to 11 years (IQR 4.9–7.7 years) in cohorts, and from 10 to 25 years (IQR 12.5–20 years) in RCTs. Populations with only negative lymph nodes were analyzed in a total of 16.7% studies. The percentage of patients who received adjuvant chemotherapy ranged from 13 to 70% for BCS and from 12 to 79% for mastectomy. The difference in OS reported at 5 years in cohorts ranged from 90.7 to 97% for BCS, and from 84.5 to 95% for mastectomy. In the RCTs, the OS at 5 years ranged from 82 to 90% for BCS, and from 79 to 92% for mastectomy. In the cohorts, the OS at 5 years ranged from 84.1 to 98.6% for BCS, and from 58.6 to 96.1% for mastectomy. From all the studies, a total of 15 (50%) studies reported better OS in the BCS group; all of them were retrospective cohorts. Only one (3.3%) study reported that mastectomy improves OS. On the other hand, the disease-free survival (DFS) in cohorts ranged from 84 to 97% for BCS, and from 82 to 91% for mastectomy. In the RCTs, the DFS ranged from 62 to 83% for BCS and from 66 to 77% for mastectomy (Table 2).

Among all the population, our results noted that BCS is associated with improved OS compared with mastectomy (RR 0.64, 95% CI 0.55–0.74). This effect was similar when analysis was performed in cohorts and multi-institutional databases (RR 0.57, 95% CI 0.49–0.67). Furthermore, the benefit of BCS was stronger in patients who had less than 10 years of follow-up (RR 0.54, 95% CI 0.46–0.64).

Of all studies included in the meta-analysis, 14 studies (46.7%) included only early-stage breast cancer patients (EBCP) that represented stages I and II.[54] We were unable to obtain the number EBCP in five studies, four cohorts,[4, 14, 47, 48] and one RCT[20]; however, from 25 studies, we identified a total of 919,584 EBCP.

Meta-analyses Results

Compared with mastectomy, BCS was associated with improved OS (RR 0.64, 95% CI 0.55–0.74) (Fig. 4). When performing the stratified analysis by study type, we found that the association was intensified in cohorts (RR 0.57, 95% CI 0.49–0.67), but it became nonsignificant in the trial subgroup (RR 1.03, 95% CI 0.96–1.10) (Fig. 5). In general, studies with retrospective cohorts included more recently published large database comparison studies that, while not prospective in design, had much larger sample sizes than the prospective trial studies. Additionally, we found that the association became more intensified with the subgroup of studies with a follow-up of less than 10 years (RR 0.54,

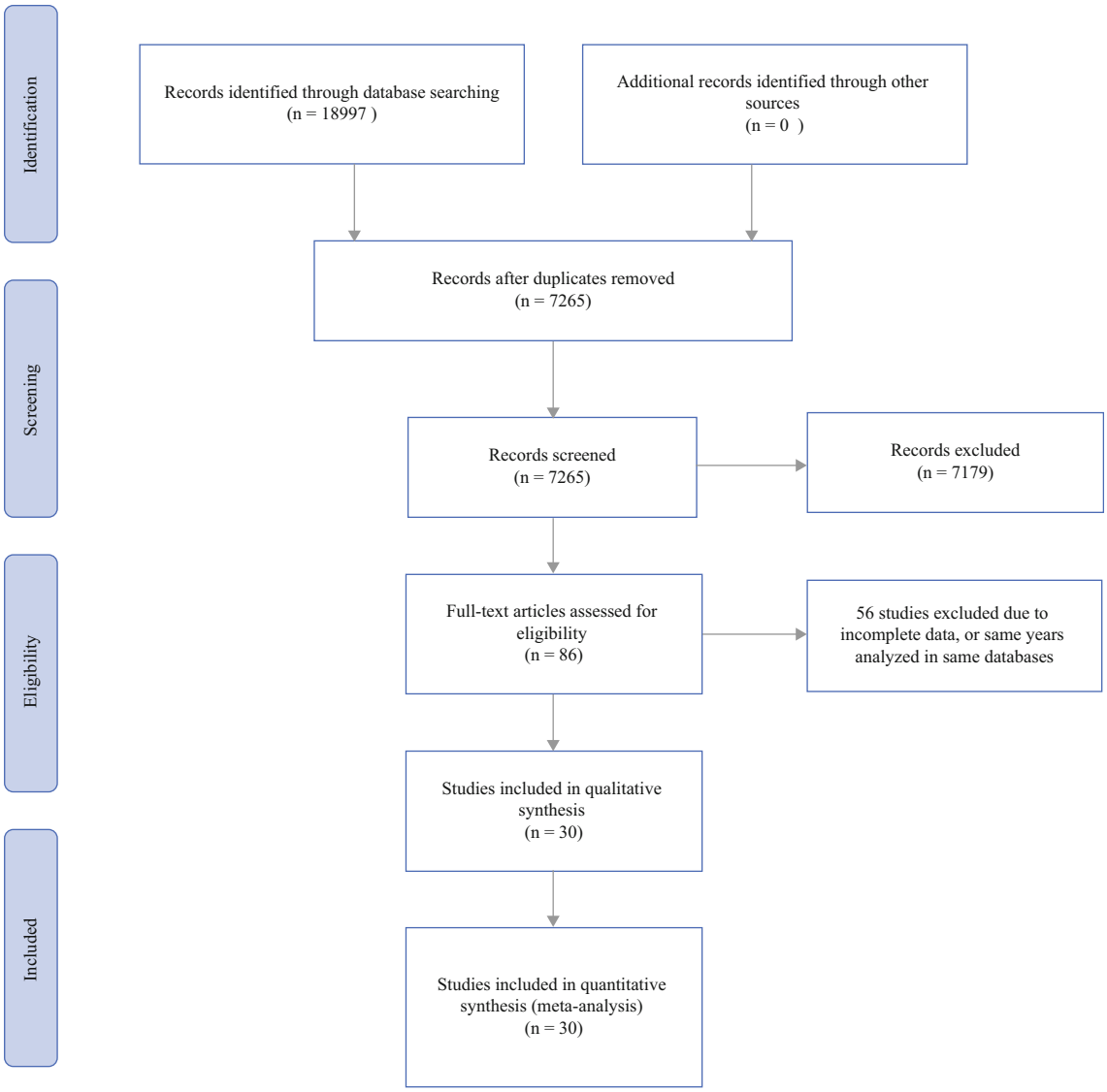

FIG. 3 Flowchart for selection of studies

95% CI 0.46–0.64); however, this was not significant in those with a follow-up of 10 years or more (RR 0.91, 95% CI 0.76–1.10) (Fig. 6). Upon performing additional analysis without the studies with high influence in the heterogeneity of the analysis, we obtained similar results with benefit of BCS over mastectomy in overall survival (Supplementary Material 2).

Regarding the DFS, only 11 studies reported this outcome. A total of 37,486 and 21,419 patients underwent BCS and mastectomy, respectively. We found that there was no difference between BCS and mastectomy (RR 0.86, 95% CI 0.60–1.22) (Fig. 7).

Risk of Bias

Regarding the cohorts (Table 3), all studies had low risk of bias (eight to nine points in the overall evaluation). Regarding the trials (Fig. 8), the majority had some concerns in the domain of selection of the reported results because the protocol was not available; however, the other domains had low risk of bias.

DISCUSSION

This meta-analysis, which included a total of 30 studies including 1.8 million women, found that women with early breast cancer who underwent BCS had better OS compared

TABLE 1 Characteristics of the included studies, treatment, and outcomes

Number	Author	Year of publication	Design	Country	Inclusion criteria	Exclusion criteria (main)
1	Almahariq	2020	Non-trial	USA	All patients with non-metastatic, early-stage, node-negative (pT1–2, pN0, cM0) breast cancer [International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography code C50.00-C50.09], diagnosed between 2006 and 2014	Male, DCIS only, $\leq$ 3 months follow-up, mortality $\leq$ 90 days of surgery, missing distance to an accredited facility, multiple cancers, $>$ 90 days between diagnosis and surgery, absence of negative margin no regional nodal evaluation; unknown chemotherapy status, laterality, radiotherapy treatment; lumpectomy alone, regional nodal irradiation, radiotherapy doses outside the range of 40–66 Gy
2	Arndt	2008	Non-trial	Germany	Breast cancer diagnosed between October 1996 and February 1998 histologically confirmed invasive breast cancer, age 18–80 years, and sufficient knowledge of the German language	Patient not complying with the inclusion criteria
3	Bhoo-Pathy	2015	Non-trial	Malaysia, Singapore, Hong-Kong	Female patients with TNBC	Stage IV, BCS without RT and unknown chemo and/or radiotherapy status
4	Chen	2015	Non-trial	USA	Female patients with T1–2N0–3M0 breast cancer with diagnosis after 2004. Infiltrating ductal breast carcinoma (histology coding 8500) with confirmed pathology diagnosis. Patients with grossly and microscopically negative margins	Patients with previous diagnosis of breast cancer or any malignant tumors (in this study, patients with sequence number code of 00 or 01 were included) Pure DCIS or stage 0 disease, bilateral breast cancer, tumor size larger than 5 cm, history of R or who do not received RT after BCS, previous chemotherapy
5	Corradini	2019	Non-trial	Germany	Tumor stages pT1pN0, pT2pN0, pT1pN1 and pT2pN1 (all M0)	pT3 or more than 3 positive lymph nodes (pN2), as RT (PMRT), neoadjuvant chemotherapy, or in case of histology of ductal carcinoma in situ (n = 1412), lymphoma (n = 10) or sarcoma (n = 57), or in case of unknown date of initial diagnosis
6	de Boniface	2021	Non-trial	Sweden	Primary invasive breast cancer from 1 January 2008, until 31 December 2017 who underwent breast surgery with known surgery date, known tumor size of up to 50 mm (T1–2), no more than 10 positive lymph nodes (N0–2), and available data on planned or given adjuvant RT	BCS not receiving RT
7	de Boniface	2018	Non-trial	Sweden	Primary unifocal, clinically node-negative invasive breast cancer smaller than 30 mm in diameter at preoperative staging	Neoadjuvant chemotherapy and/or RT, pregnancy, previous allergic reaction to blue dye or isotope, previous ipsilateral breast surgery and suspected tumor multifocality
8	De-la-Cruz-Ku	2020	Non-trial	Peru	Female patients with TNBC treated with either BCS or TM from 2000 to 2014; patients with unilateral tumor stage I–IIa; patients with adjuvant radiotherapy after BCS	Patients without adjuvant chemotherapy after BCS or TM and loss of follow-up after surgery.
9	Hartmann-Johnsen	2015	Non-trial	Norway	T1–2 N0–1 M0 and stratified into T1N0M0, T2N0M0, T1N1M0, and T2N1M0 (tumor size B 5 cm and 0–3 ipsilateral axillary nodes with metastasis).	Women with previous cancer, diagnosed with more than one primary breast cancer in same or contralateral breast within 3 months, final BCS receiving RT more than 365 days after diagnosis, women who received

Table 1 (continued)

Number	Author	Year of publication	Design	Country	Inclusion criteria	Exclusion criteria (main)
						radiotherapy after MTX when nodal axillary status was negative, and women who died within 3 months after primary operation
10	S Hofvind	2015	Non-trial	Norway	50–69 years diagnosed with primary invasive breast cancer without distant metastasis who underwent either BCS or MTX, 2005–2011	Carcinoma in situ (ductal and lobular)
11	Kim	2021	Non-trial	Korea	Female with primary invasive pathologically staged T1–2, N0–1, M0 breast cancer from the KBCR who were diagnosed between 1998 and 2012	Primary carcinoma in situ, who received neoadjuvant systemic therapy, with unknown information or tumor characteristic needed for 1:1 matching, patients who received post MTX RT, and who did not receive RT following BCS
12	Kurian	2014	Non-trial	USA	First primary breast cancer (ICD–Oncology, 3rd edition, morphology codes C50.0–50.9), of AJCC stages 0–III, from 1 January 1998 through 31 December 2011	Tumor > 5 cm or unknown, microscopic or diffuse tumor, Paget disease of breast or mammographic diagnosis only, or inflammatory carcinoma; no pathology report confirmation: unknown lymph node involvement; surgery other than bilateral MTX, breast-conserving surgery with radiation, or unilateral MTX; and diagnosis of bilateral tumors or a second primary breast tumor within 60 days
13	Lagendijk	2018	Non-trial	Netherlands	Patients with T1–2N0–2M0	Patients treated with primary (neoadjuvant) systemic therapy, breast-conserving surgery without RT, patients diagnosed with Paget's disease, ductal (DCIS) or lobular carcinoma in situ (LCIS)
14	Landescasper	2019	Non-trial	USA	Stage I–III breast cancer in the NCDB (2004–2013)	Receipt of neoadjuvant radiation, no receipt or unknown type/date of surgery or tumor size, unknown vital status for OS or time to last contact, non-primary breast cancer histologic codes prior cancer diagnosis, bilateral cancer, or surgery more than 6 months after diagnosis
15	Mahmood	2011	Non-trial	USA	Female patients, ages 20–39 years old, diagnosed with T1–2, N0–1, M0 breast cancer between 1990 and 2007, who underwent either BCS (lumpectomy and radiation treatment) or MTX	Prior history of malignancy, lumpectomy without adjuvant radiation or with unknown extent of surgery and/or radiation, poor performance status and/or those who died as a result of surgery or chemotherapy, or within 6 months of diagnosis
16	T Onega	2018	Non-trial	USA	Women diagnosed with nonmetastatic breast cancer (stage 0–III) from February 2005 to June 2010	Death before 2011 but not in Medicare
17	Onitilo	2014	Non-trial	USA	The Marshfield Clinic/St. Joseph's Hospital Cancer Registry was queried for female patients diagnosed with stage I–III breast cancer at any of the cancer center sites contributing data to the Cancer Registry using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes C50.0–C50.9 with first date of diagnosis between 1 January 1994 and 31 December 2012	Stage 0 and stage IV, second primary cancer, BCS not receiving RT

Table 1 (continued)

Number	Author	Year of publication	Design	Country	Inclusion criteria	Exclusion criteria (main)
18	Ratosa	2021	Non-trial	Slovenia	Patients with stage I–IIA (T1–2N0 or T0–1N1) breast cancer diagnosed between 2001 and 2013 and treated with upfront BCS or MTX only with or without reconstruction	No data
19	van den Broek	2018	Non-trial	Germany	Patient with invasive breast cancer diagnosed < 50 years and treated between 1970 and 2003	Patients with synchronous bilateral breast cancer and/or metastasis at or within 3 months after diagnosis
20	Van Maaren	2016	Non-trial	Netherlands	Female patients diagnosed with primary invasive, pathologically staged T1–2, N0–1, M0 breast cancer (morphology codes 8500–8575, excluding Paget's disease of the nipple) between 1 January 2000 and 31 December 2004	Primary carcinoma in situ, RT after MTX, BCS who did not receive RT, primary systemic therapy, were treated in foreign or unknown hospitals, or had undifferentiated tumors or macroscopic residual tumors
21	Vinh-Hung	2002	Non-trial	USA (SEER) – Belgium authors	Partial/less than total MTX or modified radical/total (simple) MTX; non-inflammatory histology confirmed invasive carcinoma with primary tumor confined to the breast; tumor < 5 cm; no bilateral involvement, axillary dissection performed, no internal mammary node involved, no distant metastasis	Halsted or extended MTX, unknown race, discrepancy between the reported extent of axillary nodal involvement and the reported number of nodes involved
22	Yood	2008	Non-trial	USA	Women aged 65 years or older receiving MTX or breast-conserving surgery (BCS) to treat unilateral early stage [American Joint Commission on Cancer (AJCC) TNM stages I, IIA, or IIB] breast cancer newly diagnosed from 1 January 1990 to 31 December 1994	Women with a clinically active malignancy (except nonmelanoma skin cancer) diagnosed within 5 years before or 30 days after breast cancer diagnosis
23	Yoo	2020	Non-trial	Korea	Patients with pathologic N1 breast cancer	Patients with non-AT chemotherapy, BCS without adjuvant RT and PMRT, and insufficient medical records.
24	Li	2020	Non-trial	USA (SEER) – Chinese authors	T1–2N0M0 TNBC diagnosed between 2010 and 2014	No data
25	Fisher	2002	Trial	USA 1976–1984	Women with invasive breast tumors that were 4 cm or less in their largest diameter and with either negative or positive axillary lymph nodes, confined to the breast or breast and axilla; tumors movable in relation to the underlying muscle and the chest wall; axillary nodes movable in relation to the chest wall and neurovascular bundle; no arm edema	Previous chemotherapy except for basal or squamous cell skin tumor, bilateral tumor, tumor r skin ulceration > 2 cm.; if there was peau d'orange involving more than one-third of the skin of the breast or if satellite or parasternal nodules, fixation of axillary lymph nodes (over 2 cm) or lymph nodes elsewhere suspected of containing tumor unproved by biopsy
26	Sarrazin	2003	Trial	France NCI trial	Unilateral infiltrating breast cancer of 20 mm or less at time of surgery before fixation or less at mammography	Patients over 70 years of age, pregnant women, those unable to receive anesthesia and extended surgery, those refusing MTX, or those with multifocal tumors or those who could not be followed up for geographic reasons
27	Veronesi	2002	Trial	Italy Milan trial	Maximal diameter of tumor of 2 cm or less on physical examination and no palpable axillary nodes	Older than 70 years, history of cancer
28	Litière	2012	Trial	UK, the Netherlands,	Tumors 5 cm or smaller and axillary node negative or positive disease (N0 = no palpable homolateral axillary lymph nodes;	Inadequate disease stage or histopathology, incomplete examination, bad physical condition

Table 1 (continued)

Number	Author	Year of publication	Design	Country	Inclusion criteria	Exclusion criteria (main)
				Belgium, and South Africa EORTC 2012	N1A = movable homolateral axillary lymph nodes, not containing growth; N1B = movable homolateral axillary lymph nodes, containing growth)	
29	Blichert-Toft	2008	Trial	Denmark DBCG-82TM	Invasive mammary carcinoma, age 69 years or younger, possibility of satisfactory cosmetic result by excision of the tumor, tumor restricted to one breast and no signs of multicentricity, and no evidence of disseminated disease assessed clinically, by chest radiography and bone scintigraphy	Paget's disease of the nipple, inflammatory cancer of the breast, and a history of previous malignancy
30	Simone	2012	Trial	USA NIH 1979–1987	Women with pathologically confirmed invasive breast tumors 5 cm or less with clinically negative or positive axillary lymph nodes	Metastatic disease or previous cancer, were a poor operative risk, or were found to have multicentric disease

Sample size (intervention/ control)	Intervention description	Neoadjuvant, adjuvant or palliative?	RT	Primary outcome	Conclusion
BCS 144,263	BCS	None	Yes	OS	BCS is associated with improved OS compared with MTX alone in women early-stage, node-negative breast cancer, especially higher in RS > 25 and > 50 years
MTX 87,379	MRM, NSP, SSP	None	None		
BCS 226	BCS	None	Yes	Quality of life	Quality of life improved statistically significantly at 5 years
MTX 89	MRM	None	No		
BCS 311	BCS	None	Yes	OS	T1–2, N0–1 TBNC, adjuvant radiotherapy is not associated with survival following breast cancer. However, adjuvant radiotherapy appears to be associated with improved survival in women with T3–4, N2–3 tumors, independent of the type of surgical procedure and chemotherapy
MTX 286	MRM	None	No		
MTX + RT 178	MRM + RT	None	Yes		
BCS 121,716	BCS	None	Yes	OS	BCS provides better OS than MTX with/without Radiotherapy
MTX 24,870	MRM	None	No		
MTX + RT 4512	MTX + RT	None	Yes		
BCS 6412	BCS	None	Yes	OS	Better OS in BCS
MTX 1153	MTX	None	No		
BCS 29,367	BCS	Yes	Yes	OS	BCS has better OS than MTX irrespective of RT
MTX - 12,413	MTX	Yes	No		
MTX + RT 7206	MTX + RT	Yes	Yes		
BCS 2338	BCS	None	Yes	OS and BCSS	Better OS and BCSS
MTX 429	MTX	None	No		
BCS 111	BCS	None	Yes	OS	Better OS in BCS

Table 1 (continued)

Sample size (intervention/ control)	Intervention description	Neoadjuvant, adjuvant or palliative?	RT	Primary outcome	Conclusion
MTX 117	MRM	None	No		
BCS 8065	BCS	None	Yes	OS and BCSS	Better OS and BCSS
MTX 4950	MTX	None	No		
BCS 5906	BCS	None	Yes	BCSS	BCS have significantly better breast cancer-specific survival and a lower risk of dying from breast cancer compared with women treated with MTX, independent of detection mode, prognostic, and predictive tumor characteristics.
MTX 3641	MTX	None	No		
BCS	BCS	None	Yes	OS	BCS is at least equivalent to TM in terms of OS
28,623					
MTX 17,147	Total MTX	None	No		
BCS 96,462	BCS	None	Yes	OS	Better OS in BCS
Unilateral MTX 68,548	Unilateral MTX	None	No		
Bilateral MTX 9907	Bilateral MTX	None	No		
BCS 72,993	BCS	None	Yes	BCSS and OS	BCS superior in BCSS and OS
MTX 56,699	MTX	None	No		
BCS 464,052	Lumpectomy	None	No data	OS	OS is similar in both groups but changes depending on stage and hormonal status
MTX 381,184	No data	None			
BCS 6640	BCS	None	Yes	OS	Similar OS
MTX 8124	No data	None	No		
BCS no RT 1066	BCS	No data	No	Mortality	Preoperative MRI do not offer cancer specific or all-cause mortality
BCS 1887	BCS	No data	Yes		
MTX 1451	MRM	No data	No data		
BCS 3340	BCS	No data	Yes	OS	Similar OS by type of surgery alone
MTX 1995	MRM, subcutaneous MTX, Simple MTX	No data	No		
BCS 1021	BCS	None	Yes	OS	Similar OS, but improved local, regional, and distant recurrence of the disease
MTX 339	MRM	None	No		
Non-carrier MTX – RT 1316	Non carrier MTX	None	No	OS	BCS offers better OS in carriers and non-carriers
Non-carrier MTX + RT 1954	Non carrier MTX	None	Yes		
Non-carrier BCS 2550	Carrier BCS	None	Yes		
Carrier BRAC1 MTX − RT 49	Carrier MTX	None	No		
Carrier BRAC1 MTX + RT 51	Carrier MTX	None	Yes		
Carrier BRAC1 BCS 91	Carrier BCS	None	Yes		
BCS 21,734	BCS	None	Yes	OS	Similar long-term mortality

Table 1 (continued)

Sample size (intervention/ control)	Intervention description	Neoadjuvant, adjuvant or palliative?	RT	Primary outcome	Conclusion
MTX 15,473	MTX	None	No		
BCS 28,461	BCS	No data	Yes	OS	Better OS for BCS
Total MTX 46,716	MRM	No data	No		
BCS 221	BCS	No data	No	OS	BCS alone has higher mortality than BCS or MTX
BCS 639	BCS	No data	Yes		
MTX 977	No data	No data	No		
BCS 1047	BCS	None	Yes	OS	No differences in OS, DFS, LRFFS, and RFFS between BCS and MRM alone under the AT chemotherapy regimen for patients with pN1 non-breast cancer
MTX 427	MRM	None	No		
BCS 7381	BCS	None	Yes	OS and BCSS	Better OS and BCSS in the BCS group, MTX with/out RT had similar rates
MTX + RT 562	No data	None	Yes		
MTX 6967	No data	None	No		
BCS no RT 634	Lumpectomy alone	None	No	OS	Radiation therapy was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes and by increasing follow-up, overall mortality becomes less indicative of mortality related to breast cancer
BCS 628	BCS	None	Yes		
MTX 589	MRM	None	No		
BCS 88	BCS	Yes	No data	OS	Similar in both groups
MTX 91	MRM	No	No data		
BCS 352	BCS	None	Yes	OS	No difference
MTX 349	Halsted procedure	None	No		
MTX 420	MRM	No	No		
BCS 448	BCS	No	Yes	OS	No difference
MTX 420	MRM	No	No		
BCS 381	BCS	None	Yes	RFS	No difference
MTX 350	MRM	None	No		
BCS 121	BCS	None	Yes	OS	Similar long-term mortality
MTX 116	MRM	None	No		

BCS breast-conserving surgery and radiotherapy, *RT* radiotherapy, *OS* overall survival, *RFS* recurrence-free survival, *MTX* mastectomy, *TNBC* triple-negative breast cancer

TABLE 2 Characteristics of the population and results of the included studies

Number	Author	Year of publication	Design	Age (mean or median)	Follow-up time—years (median)	Menopausal status	Stage, %	Adjuvant chemotherapy	Median OS/DFS
1	Almahariq	2020	Cohort	**BCS** 61 median	**BCS** 4.0	No data	pT1–2 pN0	**BCS** 41,294 (28.6%)	**OS BCS** < 50 years with 5- and 7-year of 97.2% and 95% > 50 years with 5- and 7-year of 93.7% and 88.4% **OS MTX** < 50 years with 5- and 7-year OS 96.9% and 95.1% > 50 years 5- and 7-year of 90.3% and 82.5% **DFS at 5 and 10 years** not available
				MTX 59 median	**MTX** 3.9	No data		**MTX** 113,753 (78.9%)	
2	Arndt	2008	Cohort	**BCS** 56 mean **MTX** 62.1 mean	5	No data	AJCC I–II	**BCS** 106 (47%) **MTX** 31 (35%)	**MTX** 5-year 23 deaths (n = 89) **BCS** 5-year 35 deaths (n = 226) **DFS at 5 and 10 years** not available
3	Bhoo-Pathy	2015	Cohort	**BCS** 49 median **MTX** 59 median **MTX + RT** 53 median	5.4	No data	TNBC I–III	**BCS** 144 (13%) **MTX** 23 (6.8%) **MTX + RT** 84 (20.4%)	**OS BCS** 5-year RS 84.1% **OS MTX** 5-year RS 58.6 % **OS MTX + RT** 5-year RS 62.7% **DFS at 5 and 10 years** not available
4	Chen	2015	Cohort	60 median	3.6	No data	AJCC I–III	**BCS** 57,580 (45.5%) **MTX** 12,002 (45.9%) **MTX-RT** 7025 (85.9%)	**OS BCS** 5-year 93.2%, 8-year 86.5% **OS MTX:** 5-year 83.5%, 8-year 72.3% **DFS at 5 and 10 years** not available
5	Corradini	2019	Cohort	**BCS** 58.2 median **MTX** 59.3 median	7.9	No data	pT1/2pN0/1	**BCS** 1831 (28.6%) **MTX** 298 (25.8%)	**1. Entire cohort: OS BCS** 5-year 95.2%, **OS MTX**: 5-year 90.5%, **OS BCS**: 10-year 86.7%, **OS MTX**: 5-year 77.6%. **2. Case control: OS BCS**: 5-year 93.8% **OS MTX**: 5-year 92.2%, **OS BCS**: 10-year 85.3%, OS **MTX**: 10-year 79.3%. **DFS at 5 and 10 years** not available
6	de Boniface	2018	Cohort	**BCS** 58 median **MTX** 63 median	13	No data	T1 (<30 mm) N0	**BCS** 489 (20.9%) **MTX 52** (12.1%)	**Entire cohort**: **OS BCS** 13-year 79.5% **OS MTX** 13-year: 64.3%. **DFS at 5 and 10 years** not available
7	De Boniface	2021	Cohort	**BCS** 62 median **MTX** 68 median	6.3	No data	T1–2, N0–2	**BCS** 8168 (27.8%) **MTX − RT** 2727 (22.0%) **MTX + RT** 4377 (60.7%)	**OS BCS** 5-year 95.1%, 10-year: 87.3%, 5 y

Table 2 (continued)

Number	Author	Year of publication	Design	Age (mean or median)	Follow-up time—years (median)	Menopausal status	Stage, %	Adjuvant chemotherapy	Median OS/DFS
				MTX + RT 59 median					**OS MTX** 5-year 84.5%, 10 years: 67.0% **OS MTX + RT** 5-year 86%, 10-year 72.1% **DFS at 5 and 10 years** not available
8	De-la-Cruz-Ku	2020	Cohort	**BCS** 47.96 mean **MTX** 51.76 mean	8.5	**Pre-M** **BCS** 57 (51.4%) **MTX** 67 (37.9%) **Post-M** **BCS** 54 (48.6%) **MTX** 110 (62.1)	TNBC I–IIa	**BCS** 111 (100%) **MTX** 177 (100%)	**OS BCS**: 5-year 88%, 10-year 85% **OS MTX**: 5-year 86%, 10-year 81% **DFS BCS** 10-year 83% **DFS MTX** 10-year 80%
9	Hartmann-Johnsen	2015	Cohort	Median age was not reported	6.9	No data	T1–2, N0–1 M0	Not measured, reported as a cofounder	**OS BCS** 5-year 95%, 10-year 86% **OS MTX** 5-year 80%, 10 year 64% **DFS at 5 and 10 years** not available
10	Hofvind	2015	Cohort	**BCS** 59.6 mean **MTX** 59.2 mean	7	No data	pT1–T3, N0–1, M0	**BCS** 33% **MTX** 56.5%	**OS BCS** 2-year 99.5%, 4-year 98.6%, 6-year 97.1% **OS MTX** 2-year 97.7%, 4-year 93.4%, 6-year 89.3% **DFS at 5 and 10 years** not available
11	Kim	2021	Cohort	Median age was not reported	10	No data	T1–2, N0–1, M0	Systemic therapy was not analyzed	**OS BCS**: 5-year 95.8%, 10-year 85% **OS MTX**: 5-year 91.6%, 10-year 81% **DFS BCS** 10-year 95.3% **DFS MTX** 10-year 94.1%
12	Kurian	2014	Cohort	Median age was not reported	10	No data	AJCC I–III	Adjuvant chemotherapy was not described separately but as a whole with or without RT	HR reported but not OS, mortality rate BCS 10-year 16.8% Mortality rate MTX 10-year 20.1% DFS at 5 and 10 years not available
13	Lagendijk	2018	Cohort	**1999–2005 cohort** **BCS** 57 Median **MTX** 62 Median	1999–2005 cohort: BCS 12.0, MTX 11.2 2006–2012 cohort:	No data	T1–2N0–2M0	**1999-2005** **Hormonal therapy** **BCS** 26.6% **MTX** 17.1% **Chemotherapy**	HR reported but not OS **1999–2005** Mortality in total BCS 28.4% Mortality in total MTX 48.2% **2006–2012**

Table 2 (continued)

Number	Author	Year of publication	Design	Age (mean or median)	Follow-up time—years (median)	Menopausal status	Stage, %	Adjuvant chemotherapy	Median OS/DFS
				2006–2012 cohort: BCS 59 Median **MTX** 61 Median	BCS 6.1 MTX 5.9			**BCS** 14.1% **MTX** 16.4% **2006-2012** **Hormonal therapy** **BCS** 20.7% **MTX** 28.4% **Chemotherapy** **BCS** 9.9% **MTX** 11.5%	Mortality in total BCS 8.9% Mortality in total MTX 19.8% DFS at 5 and 10 years not available
14	Landercasper	2019	Cohort	No median or media, presented in group analysis	10	No data	I–III	**Lumpectomy** 170,028 (45.2%) **MTX** 206,390 (54.8%)	**OS BCS**: 5-year 90.7%, 10-year: 77.5% **OS MTX**: 5-year 84.5%, 10-year: 68.3% **DFS at 5 and 10-year** not available
15	Mahmood	2011	Cohort	No media o median < **33 MTX** 2146 (57%) **BCS** 1637 (43%) **34–36 MTX** 2387 (56%) **BCS** 1910 (44%) **37–38 MTX** 2225 (54%) BCS 1900 (46%) > **39 MTX** 1366 (53%) **BCS** 1193 (47%)	5.7	No data	T1–2 N0–1M0	Author report to be unable to account for systemic therapies	**OS BCS**: 5-year 92.5%, 10-year 83.5%, 15-year 79.1% **OS MTX**: 5-year 91.9%, 10-year 83.6%, 15-year: 79.1% **DFS at 5 and 10 years** not available
16	T Onega	2018	Cohort	Distributed by category, no mean/median	5	No data	Stage I–III	No reported	HR reported but not OS DFS at 5 and 10 years not available
17	Onitilo	2014	Cohort	**BCS** 63 median **MTX** 60 median	4.75	No data	Stage I–IV Stage IV 0.5% BCS 2.2% MTX	**BCS Chemo** 930 (27.9%), **Endo** 2233 (67.4%) **MTX Chemo** 922 (46.3%), **Endo** 1181 (59.6%)	**OS BCS** 3-year 90.3%, 5-year 92.8%, 10-years, 84.7% **OS MTX** 3-year 86.8%, 5-year: 72.4%, 10-year: 65.1% **DFS at 5 and 10 years** not available

Table 2 (continued)

Number	Author	Year of publication	Design	Age (mean or median)	Follow-up time—years (median)	Menopausal status	Stage, %	Adjuvant chemotherapy	Median OS/DFS
18	Ratosa	2021	Cohort	**BCS** 61 median **MTX** 61 median	4.6	No data	Stage 1–2a	**BCS** 271 (26.5%) **MTX** 140 (41,7%)	**OS BCS** 5-year 97%, 10-year 93% **OS MTX** 5-year 95%, 10-year 89% **DFS BCS** 5-year 97%, 10-year 96% **DFS MTX** 5-year 91%, 10-year 90%
19	van den Broek	2018	Cohort	**BCS** 43 median **MTX** 43 median	13	No data	I–III	**BCS** 896 (39.6%) **MTX-RT** 363 (35.5%) **MTX + RT** 1076 (68.9%)	**OS BCS** 5-year 89%, 10-year 78% **OS MTX** 5-year 88%, 10-year 77% **MFS BCS** 5-year 84%, 10-year 75% **MFS MTX** 5-year 82%, 10-year 71%
20	Van Maaren	2016	Cohort	Distributed by category, no mean/median	11.4	No data	T1–2, N0–1, M0	**Hormonal therapy** **MTX** 4017 (26%) **BCS** 3834 (18%) **Chemotherapy** **MTX** 1864 (12%) **BCS** 2778 (13%)	**2000–04 cohort at median follow-up 11.4 years** **BCS** 16,686 (77%) **MTX** 9229 (60%)
21	Vinh-Hung	2002	Cohort	Mean age defined by stage, values from 54–62	4.2	No data	Stage T1–T2, node negative or node positive.	Information on systemic treatment was not available	**OS BCS** 5-year 89.9% ± 0.2% **OS MTX** 5-year 81.9% ± 0.2% **DFS at 5 and 10 years** not available
22	Yood	2008	Cohort	Distributed by category, no mean/median	10	No data	Stage I–II	**MTX** 119 (74%) **BCS** 40 (25%) **BCS** 2(1%)	**OS MTX** 10-year 52% **OS BCS** 10-year 8% **OS BCS** 10-year 40% **DFS at 5 and 10 years** not available
23	Yoo	2020	Cohort	**BCS** 48.1 ± 8.9 mean **MTX** 48.7 ± 9.3 mean	5.75	**Pre-M** **MTX** 289 (59.8%) **BCS** 415 (61.4%) **Post-M** **MTX** 160 (40.2%) **BCS** 261 (38.6%)	pN1	All patients receive chemotherapy	**OS BCS** 5-year 98.6% **OS MTX** 5-year 96.1% **DFS BCS** 5-year 93.3% **DFS MTX** 5-year 89.7%
24	Li	2020	Cohort	**BCS** 61 median **MTX** 59 Median	5	No data	T1–2N0M0 TNBC	**BCS** 5165 (70%) **MTX** 4,315 (61.9%) **MTX+RT** 498 (88.6%)	**OS BCS** 5-year 88.6% **OS MTX** 5-year 83.0% **OS MTX+RT** 79.6%

Table 2 (continued)

Number	Author	Year of publication	Design	Age (mean or median)	Follow-up time—years (median)	Menopausal status	Stage, %	Adjuvant chemotherapy	Median OS/DFS
				MTX + RT 53 Median					**DFS at 5 and 10 years** not available
25	Fisher	2002	RCT	60% ≥ 50 years (no media or median reported)	20	No data	I–II	34%	**OS MTX** 20-year 47 ± 2% **OS BCS-RT** 20-year: 46 ± 2% **OS BCS** 20-year: 46 ± 2% **DFS MTX** 5-year 161 (74%), 10-year 38 (17%), 20-year 36 ± 2 % **DFS BCS-RT** 5-year 187 (70%), 10-year 55 (20%), 20-year 35 ± 2 % **DFS BCS** 5-year 133 (62%), 10-year 49 (23%), 20-year 35 ± 2 %
26	Veronesi	2002	RCT	**BCS** 50 ± 10.4 mean **MTX** 51 ± 10.1 mean	20	**Pre-M** **MTX** 53.9% **BCS** 56.8% **Post-M** No data	T1–N0	All with positive axillary nodes (33)	**OS MTX** 20-year 41.2% **OS BCS** 20-year 41.7% **DFS at 5 and 10 years** not available
27	Sarrazin	2003	RCT	No median reported **BCS** ≥ 50 years 56–88 years **MTX** ≥ 50-year 59– 91 years	10	No data	Unilateral infiltrating breast cancer < 20 mm	None received chemo- or endocrine therapy	**OS BCS** 5-year 90% **OS MTX** 5-year 92% **DFS BCS** 5-year 83% **DFS MTX** 5-year 77%
28	Blichert-Toft	2008	RCT	**BCS**: 51.5 median **MTX**: 52.0 median	20	**Non-**	**randomized** **Pre-M** 63% **Post-M** 37% Randomized **Pre-M** 59% **Post-M** 41%	Not mentioned	**High-risk group** (tumor > 5 cm) 202 (31%)
OS BCS	5-year 82%, 20-year 57.8% **OS MTX** 5-year 79%, 20 year 50.6%								

Table 2 (continued)

Number	Author	Year of publication	Design	Age (mean or median)	Follow-up time—years (median)	Menopausal status	Stage, %	Adjuvant chemotherapy	Median OS/DFS
	DFS BCS 5-year 70%, 10-year 59.5% **DFS MTX** 5-year 66%, 10-year 61.1%								
29	Litiere	2012	RCT	< **50** **MTX** 156 (37%) **BCS** 175 (39%) **≥ 50** **MTX** 264 (63%) **BCS** 272 (61%)	10.9	**Pre-M** **MTX** 171 (41%) **BCS** 183 (41%) **Post-M** **MTX** 224 (53%) **BCS** 246 (55%) **Artificial-M** **MTX** 25 (6%) **BCS** 17 (4%)	Stage I–II	**Post-M** tamoxifen for 5 years **151** node-positive (adjuvant chemotherapy, hormonal therapy, or a combination of both)	**OS MTX** 15-year 53.6% **OS BCS** 15-year 51.6% **DFS at 5 and 10 years** not available
30	Simone	2012	RCT	**BCS** ≤ 50-year 47% > 50-year 53% **MTX** ≤ 50-year 46% > 50-year 54%	25	**Pre-M** **MTX** 49% **BCS** 50% **Post-M** **MTX** 51% **BCS** 50%	Tumor up to 5 cm Any N	**BCS** 39/121 (32.2%) **MTX** 42/116 (36.2%)	**OS BCS** 25.7 years 37.9% **OS MTX** 25.7 years 43.8% **DFS at 5 and 10 years** not available

RCT randomized controlled trial, *BCS* breast-conserving surgery *and* radiotherapy, *RT* Radiotherapy, *MTX* mastectomy

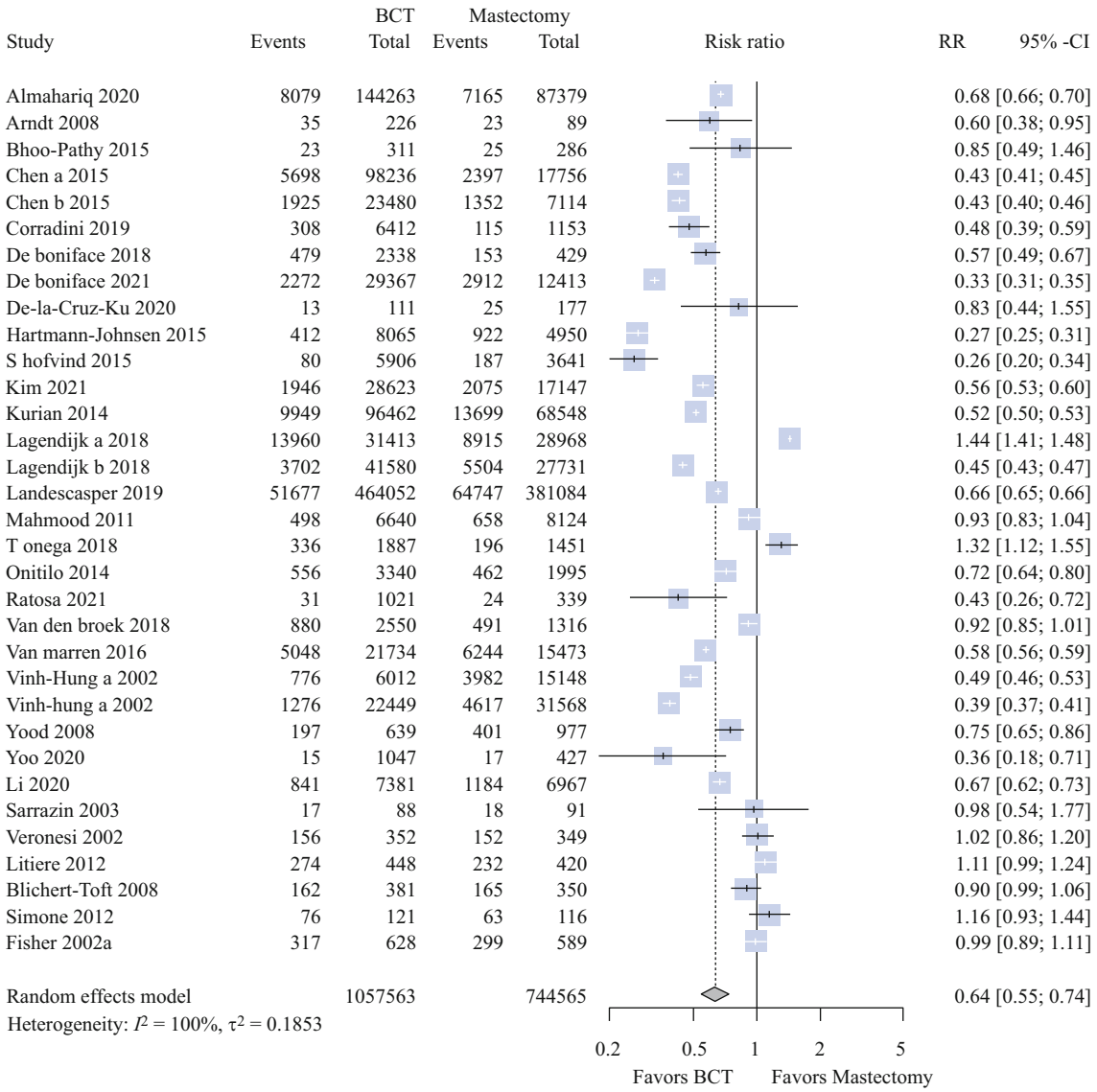

FIG. 4 Meta-analyses comparing overall survival of breast conservative surgery with radiotherapy versus mastectomy

with those who underwent mastectomy. This survival benefit was noted to be higher in studies with less than 10 years of follow-up.

Historically, BCS and mastectomy had similar overall survival rates in patients with early breast cancer. In fact, several RCTs stated that BCS had no advantage in OS over mastectomy.[17, 19, 20, 51, 53] However, more recent studies looking at large databases have demonstrated that BCT has better outcomes in OS compared with mastectomy. For example, Almahariq et al.[13] reported that OS for BCS was 97.2% compared with 93.7% for mastectomy at 5 years in patients younger than 50 years. Similarly, Chen et al.[43] reported 93.2% and 58.6%, for BCS and mastectomy at 5 years, respectively. Landercasper et al.[4] reported 90.7% and 84.5% for BCS and mastectomy at 5 years, respectively. These studies included population with breast cancer diagnosis after 2000 and a follow-up of less than 10 years.

There is a difference between the results from RCTs and cohorts. Specifically, while cohorts have a marked significant benefit of OS in patients who undergo BCT, this is not seen in RCTs. This meta-analysis is heavily weighted for cohorts, as the sum of all patients in RCTs is approximately 4000 while the cohorts have over 1.5 million patients. The latter number is likely larger given the ability of large database collections maximizing the sample sizes of cohorts studied and compared, albeit in a retrospective fashion.

The implications of these results are large, especially when discussing surgical choices with patients with breast cancer. While our study does not specifically study disease-

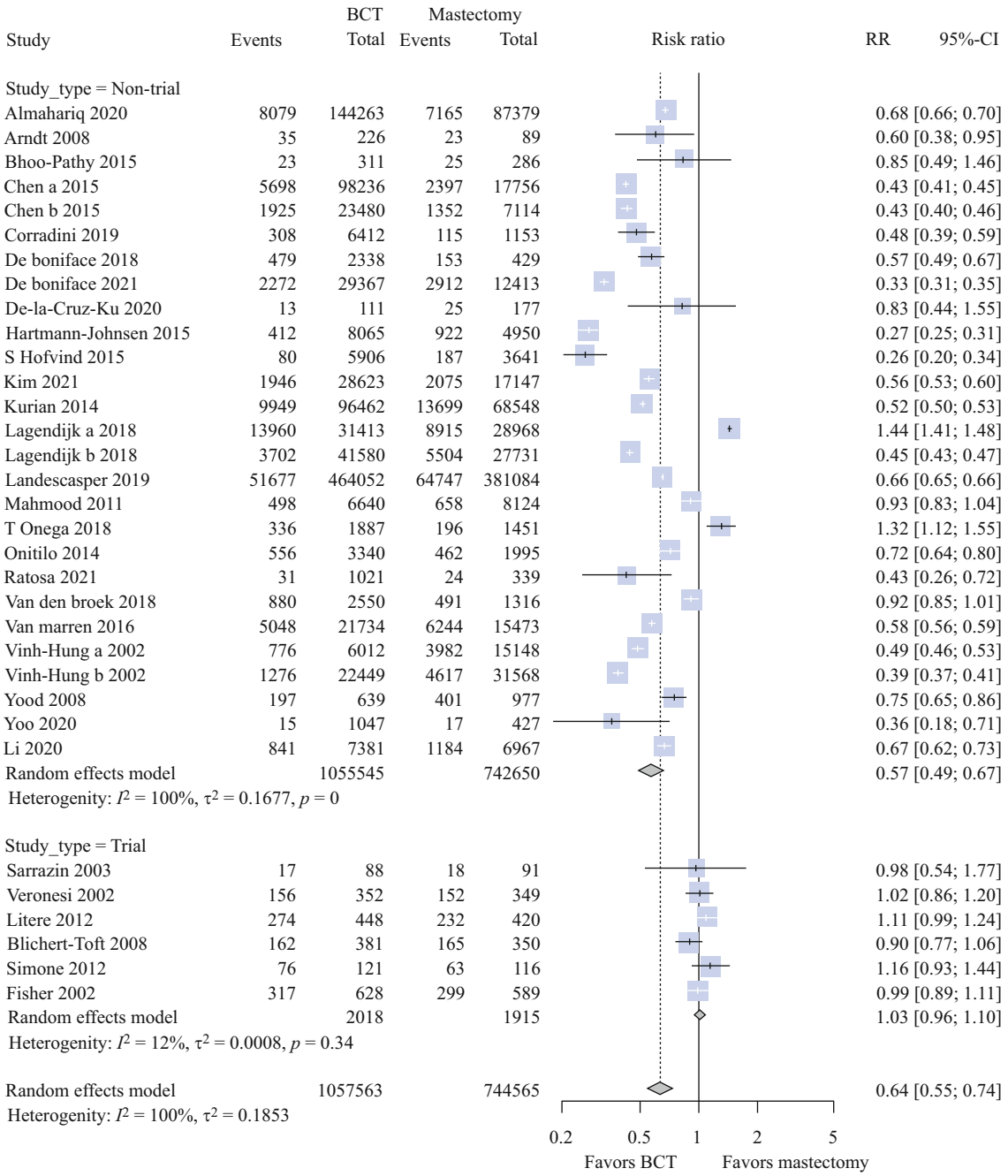

FIG. 5 Meta-analyses comparing overall survival of breast conservative surgery with radiotherapy versus mastectomy according to study type

free survival, patients should be informed that there is an overall survival difference when comparing BCT with mastectomy. First, they need to know that the samples studied included patients with early-stage breast cancer. Second, they should be informed that the data have heterogeneity, and even with attempts to control this, large sample sizes inherently study patients with variations of backgrounds and presentations. Third, patients should be informed that the true reason for an overall survival advantage with BCT is unknown. Postulations can be made that radiation therapy has improved with better planning and techniques to avoid end-organ radiation damage (deep breath holding, prone positioning, etc.), which may lead to an improvement in survival.[55, 56] Furthermore, medical therapy has also improved in decreasing mortality with a de-escalation in treatment leading to less unnecessary toxicity with a higher focus on breast cancer disease-specific care and tailored treatments.[57–59] All such adjuvant treatments have allowed for de-escalated surgery in the form of BCT to allow patients a quicker recovery, much

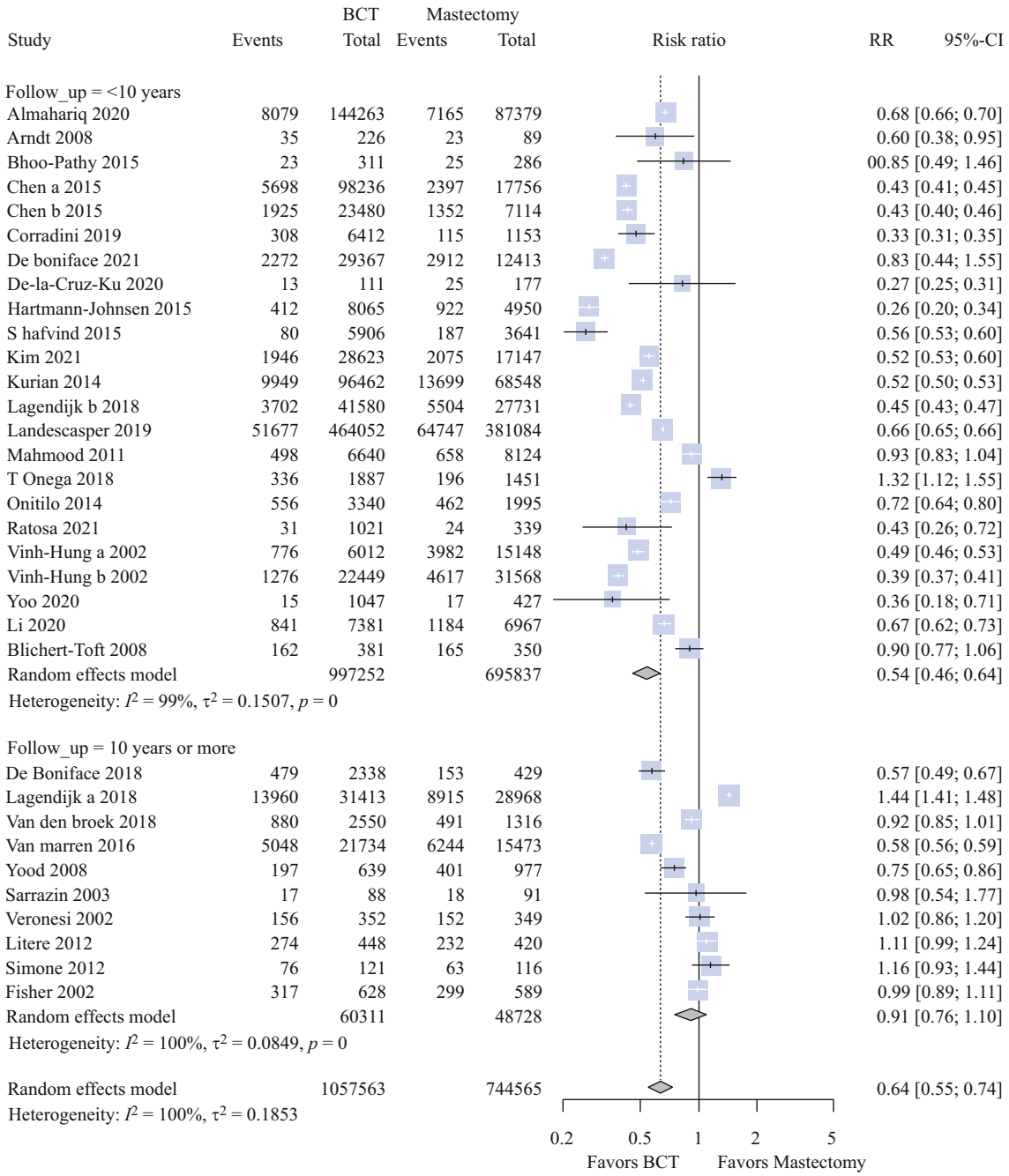

FIG. 6 Meta-analyses comparing overall survival of breast conservative surgery with radiotherapy versus mastectomy according to time of follow up

quicker than a mastectomy with or without reconstruction.[60, 61] Another factor that may contribute to this difference is the improvement with digital imaging modalities leading to earlier detection.[62–69] One counterpart of earlier diagnosis is the lead time bias that could be confounded with better OS; however, some cited studies still have the same results when adjusting to the correction factor.[14, 70]

Moreover, new prognostic factors and markers, such as Ki-67, and breast cancer gene expression assays that the National Comprehensive Cancer Network (NCCN) recommends and can help to predict the risk of recurrence and provide both prognostic and predictive information.[71] Furthermore, the increased availability for genetic testing panels can help guide surgical decision making, improve detection, and improve adjuvant therapies, which have an impact on OS. Better access to health care and information

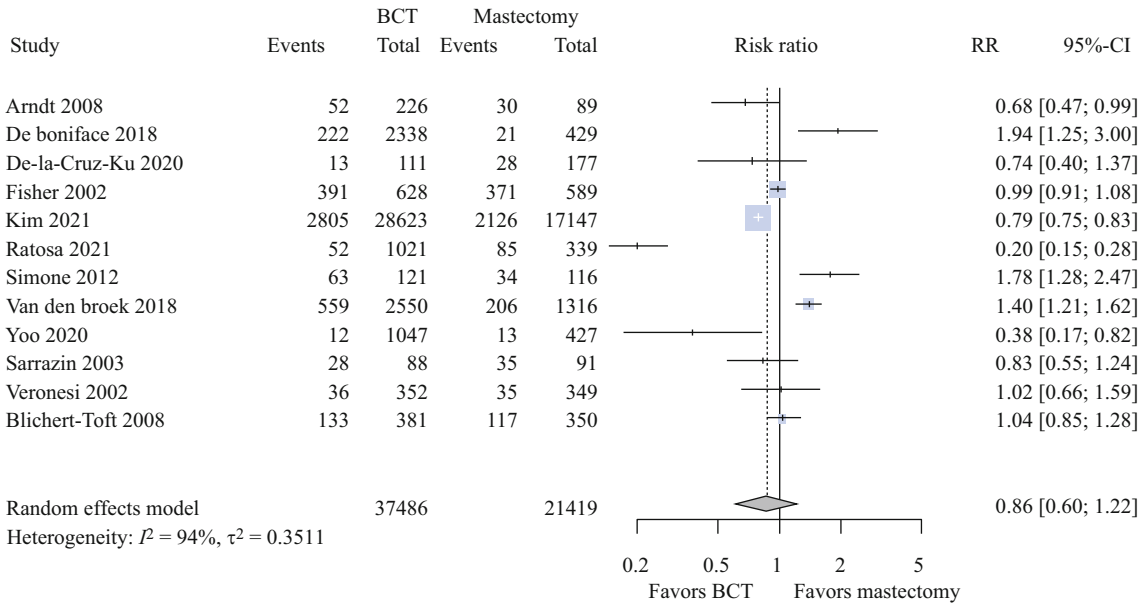

FIG. 7 Meta-analyses comparing disease-free survival of breast conservative surgery with radiotherapy versus mastectomy

allows patients to demand standards of care be followed. Often, second opinions and tumor board presentations ensure appropriate margins are taken after a partial mastectomy when in the past this may not have been as stringent.[72–74]

In 1993, the NCCN was formally incorporated, with the first clinical practice guidelines published in 1996. Since then, several changes have been made in the integral management of breast cancer.[75, 76] The early randomized controlled trials for BCT versus mastectomy were initiated prior to these guidelines. In 2013, at the Saint Gallen Conference, breast cancer classification included molecular subtypes leading to more targeted therapies.[71, 77] Identification of histologic subtypes, gene expression assays, and better targeted therapies have led to better breast cancer outcomes.[78, 79] This fact could explain the similar survival found in previous RCT studies over 25–30 years ago compared with population-based studies that include patients from 2000 to 2010.

Short-term follow-up studies showed that BCS had the same benefit but a higher impact on OS than mastectomy, compared with more than 10 years of follow-up studies. This could be explained by the same statement detailed above. Populations diagnosed in early 2000 and 2010 had similar surgical treatments; however, improvements in adjuvant therapy modalities continued to evolve, leading to better overall outcomes. Modern-day improved targeted therapies in oncology may allow for better control or even elimination of remnant disease with breast conservation, when in the past such a lack of targeted therapy would lead to possibly increased local/regional recurrence and mortality.[80–82] Proving this would be difficult and likely unethical in a prospective fashion.

Findings of this meta-analysis may have significant implications for surgical treatment of breast cancer moving forward. Given the significant 36% decreased risk of death in patients who underwent BCS, improved psychosocial well-being, improved body image, and decreased surgical morbidity, patients should be counseled on these potential benefits and surgical decisions should be shared.[83]

As with any meta-analysis, there are limitations. The limitations included within this study are limited by variability of the studies that met our inclusion criteria and the resulting heterogeneity of these studies. While we assessed each study for its quality and suitability for inclusion, it remains possible that poor-quality studies were included. There is one study that included less than 2.5% of metastatic disease in their study,[15] and another that included 15% of neoadjuvant chemotherapy in their analysis,[46] which could have a minor impact in our results. We are also subject to publication bias, as the data we are able to use come from studies that were considered for publication, and not those that may not have had significant results. In addition, it is important to acknowledge that both RCTs and cohort studies have advantages and disadvantages. RCTs have less heterogeneity and benefit of randomization; however, these were performed several decades ago. Alternatively, cohort studies included here have newer very large databases representing newer radiotherapy technology, newer adjuvant medical therapies, better control of

TABLE 3 Risk of bias of cohorts

Author	Year	Selection				Comparability	Outcome			Score
		Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome not present at the start		Assessment of the outcome	Enough follow-up	Adequate follow-up	
Kim	2021	1	1	1	1	2	1	1	1	9
de Boniface	2021	1	1	1	1	2	1	1	1	9
Ratosa	2021	1	1	1	1	2	1	1	1	9
Almahariq	2020	1	1	1	1	2	1	1	1	9
De-la-Cruz-Ku	2020	1	1	1	1	2	1	1	1	9
Yoo	2020	1	1	1	1	2	1	1	1	9
Li	2020	1	1	1	1	2	1	1	1	9
Corradini	2019	1	1	1	1	2	1	1	1	9
Landercasper	2019	1	1	1	1	2	1	1	1	9
de Boniface	2018	1	1	1	1	2	1	1	1	9
Lagendijk	2018	1	1	1	1	2	1	1	1	9
T Onega	2018	1	1	1	1	2	1	1	1	9
van den Broek	2018	1	1	1	1	2	1	1	0	8
Van Maaren	2016	1	1	1	1	2	1	1	0	8
Bhoo-Pathy	2015	1	1	1	1	2	1	1	1	9
Chen	2015	1	1	1	1	2	1	1	1	9
Hartmann-Johnsen	2015	1	1	1	1	2	1	1	0	8
S Hofvind	2015	1	1	1	1	2	1	1	1	9
Kurian	2014	1	1	1	1	2	1	1	1	9
Onitilo	2014	1	1	1	1	2	1	1	1	9
Mahmood	2011	1	1	1	1	2	1	1	1	9
Arndt	2008	1	1	1	1	2	1	1	1	9
Yood	2008	1	1	1	1	2	1	1	1	9
Vinh-Hung	2002	1	1	1	1	2	1	1	1	9

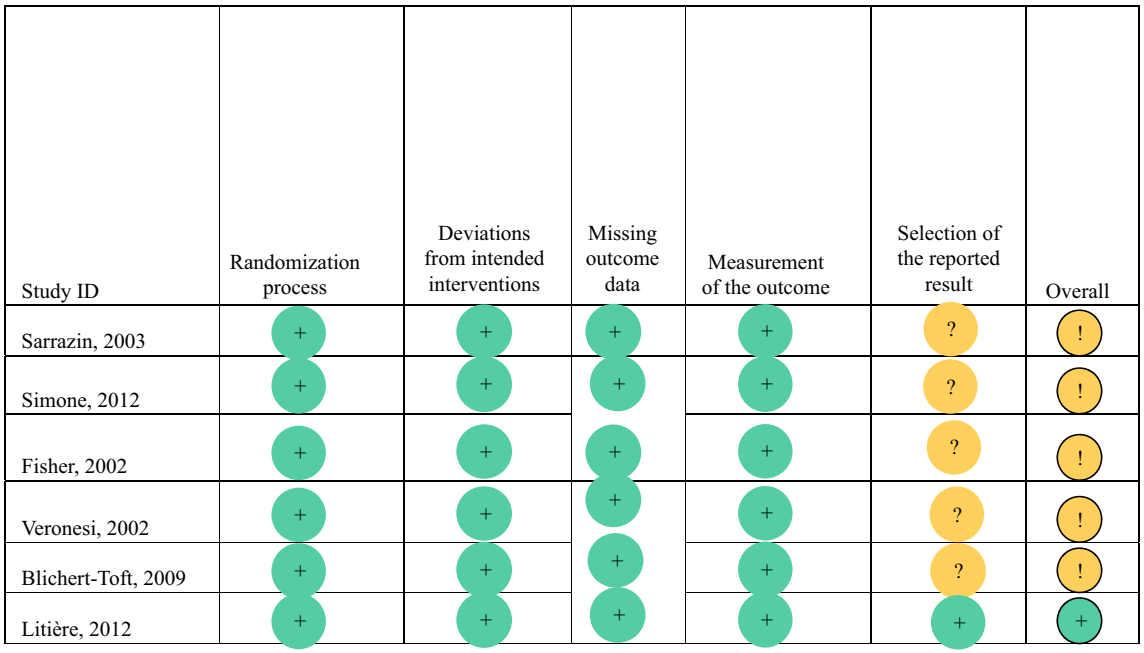

FIG. 8 Risk of bias in the included randomized controlled trials

margins following standardized guidelines, and newer surgical techniques. Additionally, large databases from around the world capture different populations, which has the added advantages of generalizability, and larger sample sizes that provide higher powers in such sizes leaving less to chance. While acknowledging limitations in both RCTs and cohort studies, the results demonstrating overall survival provide summary data that can be used by breast surgeons in a shared decision surgical decision-making scenario with patients with breast cancer. As with any meta-analysis, there is heterogeneity among studies, which is a known possible limitation. To address heterogeneity that may impact results, we performed diagnostic measures to assess outlier or influential studies within the overall pooled cohort. The outlier studies that influenced heterogeneity the most were removed, shown within the Baujat plot (Figs. 1, 2), and the results were compared (overall pooled cohort compared with the pooled cohort with excluded studies). There was minimal effect on the primary results, including relative risk, thus not impacting our outcomes, and our overall pooled cohort was used. Another limitation of our study is that stages were not balanced upfront for each type of surgery in 50% of the cohorts included. Despite multivariate analysis that adjusted for stages and still demonstrated a benefit of BCS in OS compared with mastectomy, future studies comparing survival and other key breast cancer outcomes should balance cancer stage with type of surgery performed. Similarly, another limitation is that only 29% of the cohorts had balanced breast cancer subtypes; 41% reported HER2 status, while none of the RCTs had these variables controlled, most likely owing to the new classification since the past decade. Future studies should include analysis of the subtypes that should be balanced among surgical arms. Additionally, we did not examine disease-free survival (DFS) specifically, which is equally important to consider in the care of patients with cancer. Unfortunately, too few studies ($< 50\%$) included in our meta-analysis reported disease-free survival, which prevented us from making a reliable conclusion. Future studies focusing on a search specifically for DFS may be reasonable to conduct; however, OS was much more prevalent as a studied outcome, allowing us to adjust for heterogeneity when checking for the robustness of our conclusion.

CONCLUSION

This meta-analysis demonstrates that overall survival is better in patients who undergo breast conservation therapy compared with mastectomy. These data should be considered when counseling a patient with a new diagnosis of breast cancer on their breast cancer surgical options.

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