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Systematic Review

Outcomes after breast-conserving surgery or mastectomy in patients with triple-negative breast cancer: meta-analysis

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Abstract

Background: In patients with triple-negative breast cancer (TNBC), oncological and survival outcomes based on locoregional treatment are poorly understood. In particular, the safety of breast-conserving surgery (BCS) for TNBC has been questioned.

Methods: A meta-analysis was performed to evaluate locoregional recurrence (LRR), distant metastasis (DM), and overall survival (OS) rates in patients with TNBC who had breast-conserving surgery *versus* mastectomy. Estimates were pooled in random-effects analysis. The effect of study-level co-variables was assessed by univariable metaregression.

Results: Fourteen studies, including 19 819 patients operated for TNBC met the inclusion criteria; 9828 patients (49.6 per cent) underwent BCS and 9991 (50.4 per cent) had a mastectomy. Patients with smaller tumours were more likely to be selected for BCS (pooled odds ratio (OR) for T1 tumours 1.95, 95 per cent c.i. 1.64 to 2.32; $P < 0.001$). The pooled OR for LRR was 0.64 (0.48 to 0.85; $P = 0.002$), indicating a statistically significantly lower odds of LRR among women who had BCS relative to mastectomy. The pooled OR for DM was 0.70 (0.53 to 0.94; $P = 0.02$), indicating a lower odds of DM among women who had BCS; however, this difference diminished with increasing study-level age and follow-up time. A pooled hazard ratio of 0.78 (0.69 to 0.89; $P < 0.001$) showed a significantly lower hazard for all-cause mortality among women undergoing BCS *versus* mastectomy.

Conclusion: These results should be interpreted cautiously owing to likely differences in selection for BCS or mastectomy in the included studies. Patients with TNBC selected for BCS do not, however, have a worse prognosis than those treated with mastectomy, and breast conservation can be offered when feasible clinically.

Introduction

Breast cancer classification driven by gene expression analysis has led to the identification of breast cancer subtypes associated with different clinical behaviour and treatment responses. According to the expression of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), breast cancer is divided into four major subgroups, namely luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC)[1–4]. Among these, TNBC, which accounts for 10–20 per cent of all breast cancers[5,6], is the subtype with the worst prognosis, owing to its biological aggressiveness and propensity to develop early locoregional recurrence (LRR) and distant metastasis (DM)[5,7,8].

In contrast to other subtypes, TNBC lacks individualized treatment regimens and targeted systemic therapies associated with improvements in clinical outcomes[5,9,10]. Although most studies of TNBC have focused on prognostic and predictive factors, and evolution of systemic treatments, less attention has been given to oncological outcomes in relation to locoregional treatment. Several studies demonstrated that, among patients receiving breast-conserving surgery (BCS), the TNBC and HER2-positive subtypes were associated with a higher risk of both LRR and DM compared with luminal subtypes[4,11–14]. These findings have raised some concerns regarding the safety of BCS in TNBC, which have persisted owing to conflicting results for this patient group[4,5,8,15–18]. Furthermore, it was reported that patients with TNBC with who were candidates for BCS opted for mastectomy instead[9], although there is no evidence that molecular subtype should be a selection factor for surgical treatment[4,14,19]. Thus, the use of BCS for TNBC in real-world breast practice is difficult to evaluate, and the variable risk of LRR across subtypes may be influencing the surgical decision-making process.

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Lay summary

Breast cancer represents one of the most frequent tumours in women. Triple-negative breast cancer (TNBC), which accounts for 10–20 per cent of all breast cancers, is a special subtype with the worst prognosis, because of its biological aggressiveness and propensity to develop early locoregional cancer recurrences and distant metastases after treatment. The results of the present study, based on a meta-analysis of about 20 000 women treated with breast conservation therapy or mastectomy, provides consistent evidence that women with TNBC who have breast-conserving therapy do not have a worse prognosis than those treated with mastectomy. Hence, breast-conserving surgery followed by radiotherapy may be routinely offered to women with TNBC.

The literature on this topic is heterogeneous. Some studies focused only on patients with TNBC who had BCS[8,10], whereas others also included patients who underwent mastectomy[13,20]. Most observational studies and reviews have focused on the outcomes of BCS in TNBC in comparison with other breast cancer subtypes[8,10,21,22]. To overcome these limitations, the impact of surgical treatment on oncological outcomes in patients with TNBC was evaluated here by undertaking a systematic review and meta-analysis of studies comparing BCS *versus* mastectomy in patients with TNBC. The primary endpoints were LRR, DM, and overall survival (OS) in patients who had BCS *versus* those who had mastectomy for TNBC.

Methods

Identification of studies

This work followed the PRISMA guidelines[23]. A systematic literature search of the PubMed, Web of Science, and Scopus databases was performed from January 1990 to May 2020 to identify studies reporting on the clinical outcomes of BCS and mastectomy in patients with TNBC. The following keywords were used and combined for the search: 'triple negative breast cancer', 'basal-like breast cancer', 'breast conserving surgery', 'breast conserving therapy', 'breast conservation', 'quadrantectomy', 'lumpectomy', 'wide local excision', 'mastectomy'. Reference lists were searched manually to identify additional studies.

Review of studies and eligibility criteria

To be eligible for inclusion, studies had to meet the following criteria: compare oncological outcomes or survival outcomes of BCS (breast conservation, quadrantectomy, lumpectomy, segmental mastectomy or wedge resection, plus radiotherapy (RT)) *versus* mastectomy in patients with TNBC; and report data on at least one outcome for patients not already included through another study. If data from patient registries overlapped, the most informative and/or recent article was included. Study eligibility was not restricted by whether adjuvant RT was given in the mastectomy cohort. For two studies[13,24] that reporting separately on mastectomy-alone and mastectomy + RT patient subgroups, the mastectomy-alone cohort was included in order to minimize clinical heterogeneity between studies (adjuvant RT was either not undertaken or performed in a minority of patients undergoing mastectomy in all other included studies), and to minimize the possibility of selection bias (patients with poorer prognostic features are likely to be selected for mastectomy + RT). Studies comparing BCS and mastectomy for non-TNBC subtypes, those for which it was not possible to extract TNBC data, and studies in which the outcomes of interest were not reported, or could not be derived for BCS and mastectomy groups, were excluded.

Data extraction and quality assessment

Two investigators independently extracted the following data: study design, number of patients receiving BCS and mastectomy, patient and tumour characteristics, type of surgical treatment, duration of follow-up, oncological outcomes (number of patients developing LRR, number developing DM), and survival outcomes (5-year OS, 5-year disease-free survival (DFS)). Adjusted hazard ratios (HRs) for survival outcomes were extracted when reported, and co-variables included in multivariable models were recorded. Study quality was assessed according to the Newcastle–Ottawa Scale for cohort studies[25]. Differences in extracted data were resolved through discussion and consensus.

Definition of triple-negative breast cancer

This study focused on patients with TNBC, defined as breast cancer that does not express ER or PR and does not overexpress HER2 protein[26–28]. Patients with basal-like tumours from studies that classified patients according to gene expression analysis were also included. The overlap between immunohistochemical classification and molecular subtype is not exact because approximately 75–80 per cent of tumours classified as TNBCs belong to the basal-like breast cancer group; however, TNBC and basal-like cancers are commonly regarded as synonymous especially when deciding on treatment[12,22,29].

Statistical analysis

Estimates of rates of LRR and DM were calculated for each study, and exact 95 per cent confidence intervals calculated. To compare treatment groups, log HRs for OS and log odds ratios (ORs) for LRR and DM (and their standard errors) were computed within studies. Each outcome was pooled by logistic regression using the inverse-variance method with random effects for study, according to the DerSimonian and Laird method[30], in the metafor package[31] of R version 3.6.1 (R Project for Statistical Computing, Vienna, Austria). Forest plots were generated using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). The magnitude of statistical heterogeneity was assessed by means of the I^2 statistic[30].

Variables were assessed as potential study-level confounders when reported by at least half of the included studies. Extracted variables that were reported in less than half of studies were not considered reliable for modelling. For OS, all variables (except follow-up time) meeting this criterion were included in univariable meta-regression models to assess their study-level effects on the pooled HR. For the outcomes LRR and DM, potential study-level confounders of the relationship between treatment and outcome (mean age, follow-

up, T1 category, node positivity, grade 1–2, lymphovascular invasion (LVI), positive margins, adjuvant chemotherapy, and RT) were fitted in univariable logistic metaregression models (not including treatment). In addition, for studies that reported co-variables separately for BCS and mastectomy, univariable logistic metaregression was undertaken to assess the association between each variable and treatment group. Co-variables with at least a weak association ($P < 0.100$) in either analysis were adjusted for in univariable metaregression to assess their effects on the pooled ORs for treatment (these were T1 category and LVI). Age, follow-up time, and RT were also investigated based on previous evidence of their association with LRR and DM. Sensitivity analyses were undertaken to derive unadjusted pooled estimates from subsets of studies that reported each co-variable, for comparison with adjusted estimates. Statistical significance was set at $P < 0.050$ (2-sided); $P < 0.100$ was considered weak evidence of an association.

Results

Fourteen studies[13,15,16,19,24,32–40] published between 2008 and 2019 met the eligibility criteria, and were included in the meta-analysis. A PRISMA diagram summarizing study screening and inclusion is shown in *Fig. 1*. There was 100 per cent agreement between the two data extractors. The included studies were primarily retrospective using broadly comparable clinical inclusion criteria. No randomized trials were identified.

These studies had a median of 291 patients with TNBC (range 68–14 910) treated between 1980 and 2014 (*Table 1*). A total of 19 819 patients with TNBC were included, of whom 9828 (49.6 per cent) underwent BCS and 9991 (50.4 per cent) mastectomy. Four studies[16,24,34,39] included only patients without axillary lymph node metastases (N0), whereas one study[36] included only patients with axillary node metastases (N+). Three[24,36,38]. were multicentre studies In five studies[15,19,33,38,40], adjuvant RT was used in a minority of patients undergoing mastectomy (range 25–48 per cent). As for the use of RT in the BCS cohort, the study-level median was 100 (range 91.8–100) per cent. Nine studies[13,15,16,24,32,34,36,38,39] reported on the use of adjuvant chemotherapy, which was used in 6912 patients (73.9 per cent) who received BCS and in 5923 (63.3 per cent) who underwent mastectomy (median 100 (range 51.9–100) and 100 (61.3–100) per cent in the BCS and mastectomy groups respectively). Seven[15,16,32,34,36,39,40] of 14

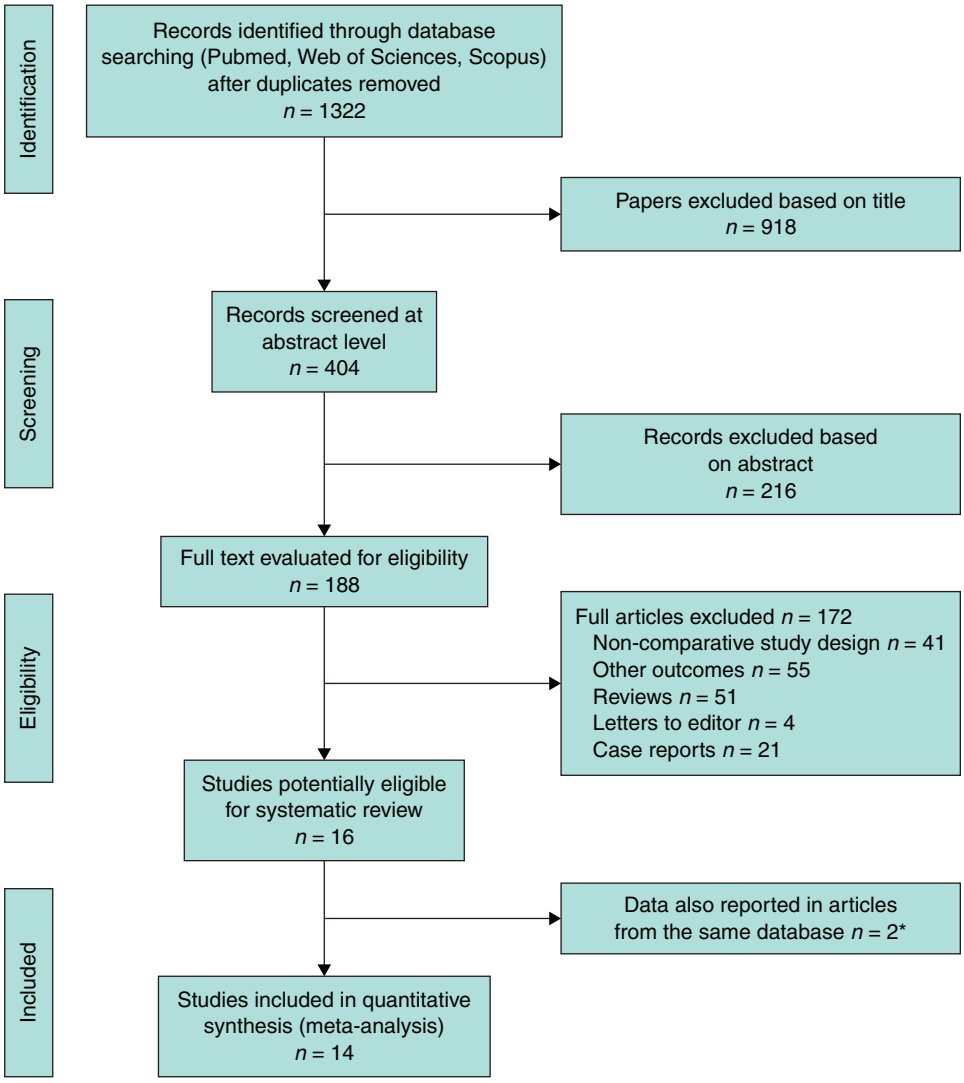

Fig. 1 PRISMA flow diagram showing selection of studies for meta-analysis

The literature search identified three articles[4,20,24] that reported data from the Surveillance, Epidemiology, and End Results programme, which is the most comprehensive source of information on cancer incidence and deaths in the USA, and covers approximately one-quarter of the entire US population. Among these, the most informative for the purposes of this review was included[24].

Table 1 Characteristics of studies included in meta-analysis

Reference	Country	Patients with TNBC		Inclusion criteria	Time frame	Study endpoints
		BCS	Mastectomy			
Abdulkarim *et al.*[13]	Canada	319	287	Patients with TNBC	1998–2008	LRR, DM, OS
Adkins *et al.*[15]	USA	651	674	Patients with TNBC who underwent primary BCS or mastectomy and adjuvant chemotherapy	1980–2007	LRR, DM, OS
De-La-Cruz-Ku *et al.*[32]	Peru	101	162	Patients with unilateral stage I–IIa TNBC RT after BCS	2000–2014	LRR, DM, OS
Dragun *et al.*[33]	USA	33	44	Patients with TNBC	2004–2009	LRR, DM
Gabos *et al.*[19] (2010)	Canada	31	41	Patients with HER2-positive or HER2-negative breast cancer	1998–2003	LRR
Ho *et al.*[34]	USA	129	65	Patients with T1a/b N0 TNBC	1999–2006	LRR, DM
Ihemelandu *et al.*[35]	USA	29	39	Black women with invasive breast cancer who had assessable IHC data for ER, PR, and HER2 status	1998–2005	LRR, DM, OS
Kim *et al.*[36]	Korea	212	108	Patients with pT1–2 N1 TNBC	2005–2010	LRR, DM
Li *et al.*[24]	China	7381	7529	Patients with T1–2 N0 M0 TNBC	2010–2014	OS
Martinez-Ramos *et al.*[37]	Spain	136	274	Patients with invasive, unilateral non-metastatic breast cancer	2000–2008	LRR
Parker *et al.*[38]	USA	61	141	Patients with stage I–III TNBC	1998–2008	LRR, DM, OS
Raghavan *et al.*[39]	India	49	121	Patients with stage I or IIA, N0 TNBC	2010–2011	LRR, DM, OS
Voduc *et al.*[40]	Canada	248	308	Patients with breast cancer	1986–1992	LRR
Zumsteg *et al.*[16]	USA	448	198	Patients with T1–2 N0 TNBC undergoing BCS or mastectomy without postmastectomy RT	1999–2008	LRR, DM, OS

TNBC, triple-negative breast cancer; BCS, breast-conserving surgery; LRR, locoregional recurrence; DM, distant metastasis; OS, overall survival; RT, radiotherapy; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; ER, oestrogen receptor; PR, progesterone receptor.

studies included in this meta-analysis reported on the sequence of drugs in chemotherapy protocols, although specific data were not reported separately for the BCS and mastectomy cohorts in most of them. Nonetheless, sequential anthracycline–taxane chemotherapy was administered in the vast majority of patients, according to guidelines regarding neoadjuvant and adjuvant treatment of TNBC.

Patients receiving neoadjuvant chemotherapy were excluded from six studies[13,15,16,34,37,40]. Among eight studies reporting on the use of neoadjuvant chemotherapy by surgery type, it was administered before mastectomy in only a minority of patients in one study (21 per cent)[38]. None of the studies administered neoadjuvant chemotherapy before BCS.

Patients in the BCS and mastectomy groups in each study were from the same time period in all studies. A median of 59.1 (range 36.8–100) and 38.1 (21.3–100) per cent of patients in the BCS and mastectomy groups respectively had T1 tumours (based on 9 studies). Respective values were 16.9 (0–100) and 10.2 (0–100) per cent for N+ disease (based on 10 studies); and 16.3 (10.3–34.4) and 25.2 (5.5–34.0) per cent for grade 1–2 tumours (based on 8 studies).

Comparison between treatment groups showed that patients with smaller tumours were much more likely to be selected for BCS than mastectomy (pooled OR for T1 category (9 studies) 1.95, 95 per cent c.i. 1.64 to 2.32; $P < 0.001$). Pooled estimates for differences between treatment groups were not statistically significant for other prognostic variables (node positivity, grade, positive margins, use of neoadjuvant chemotherapy, adjuvant chemotherapy) reported in seven or more studies (*Table 2*). Study quality is summarized in *Table S1*.

Modelled estimates for locoregional recurrence

From 12 studies[13,15,16,19,32–38,40] reporting rates of LRR with a mean follow-up of 71 (range 23–144) months, the unadjusted pooled OR for LRR was 0.64 (95 per cent c.i. 0.48 to 0.85; $P = 0.002$), showing a statistically significantly lower odds of LRR among women who had BCS relative to women who underwent mastectomy (*Fig. 2a*). There was moderate heterogeneity between studies ($I^2 = 40$ per cent). In adjusted models, no individual covariable was statistically significant (*Table 3*). However, adjustment for the proportion of patients who received RT resulted in a relatively large decrease in the adjusted OR compared with the unadjusted OR. Sensitivity analyses in which unadjusted and adjusted estimates were derived from the same subset of studies suggested that this decrease in OR was due to the smaller number of studies in adjusted models, rather than the statistical adjustment (*Table S2*).

Modelled estimates for distant metastases

From 10 studies[13,15,16,32–36,38,39] reporting DM rates with mean follow-up of 66 (range 23–102) months, the unadjusted pooled OR for DM was 0.70 (95 per cent c.i. 0.53 to 0.94; $P = 0.02$), with moderate heterogeneity ($I^2 = 40$ per cent) (*Fig. 2b*). Age ($P = 0.007$) and follow-up time ($P = 0.006$) were statistically significant in adjusted models, with increases in both variables associated with larger OR (*Table 3*). At the mean study-level age (52 years), the adjusted OR was 0.73 (0.60 to 0.90; $P = 0.003$); however, when age was centred at 55 years, the model predicted an OR of 0.91 (0.66 to 1.25; $P = 0.54$). Similarly, at the mean study-level follow-up, the adjusted OR was 0.59 (0.50 to 0.70; $P < 0.001$); when follow-up was centred at 100 months, the model predicted an OR of 1.07 (0.69 to 1.66; $P = 0.75$).

Modelled estimates for overall survival

Seven studies[13,15,16,24,32,35,38] reported HRs for OS that were adjusted at the patient level for imbalances in patient and treatment characteristics between BCS and mastectomy cohorts. The most common co-variables included in multivariable models by these studies were tumour size and/or T category (all 7 studies),

Table 2 Study-level proportions, and pooled odds ratios for comparison of co-variables between treatment groups

	No. of studies	% of patients*		Odds ratio (BCS *versus* mastectomy)†	*P* for odds ratio
		BCS	Mastectomy		
T1 tumours	9	59.1 (36.8–100)	38.1 (21.3–100.0)	1.95 (1.64, 2.32)	<0.001
N+	10	16.9 (0–100)	10.2 (0–100)	0.90 (0.44, 1.83)	0.76
Grade 1–2	8	16.3 (10.3–34.4)	25.2 (5.5–34.0)	0.83 (0.65, 1.07)	0.16
Positive margins	9	0 (0–30.7)	0 (0–39.0)	0.87 (0.13, 5.90)	0.89
Neoadjuvant chemotherapy	8	0 (0–0)	0 (0–21.3)	0.48 (0.13, 1.77)	0.27
Adjuvant chemotherapy	9	100 (51.9–100)	100 (61.3–100)	1.07 (0.74, 1.56)	0.72

*Values are median (range); †values in parentheses are 95 per cent confidence intervals. BCS, breast-conserving surgery.

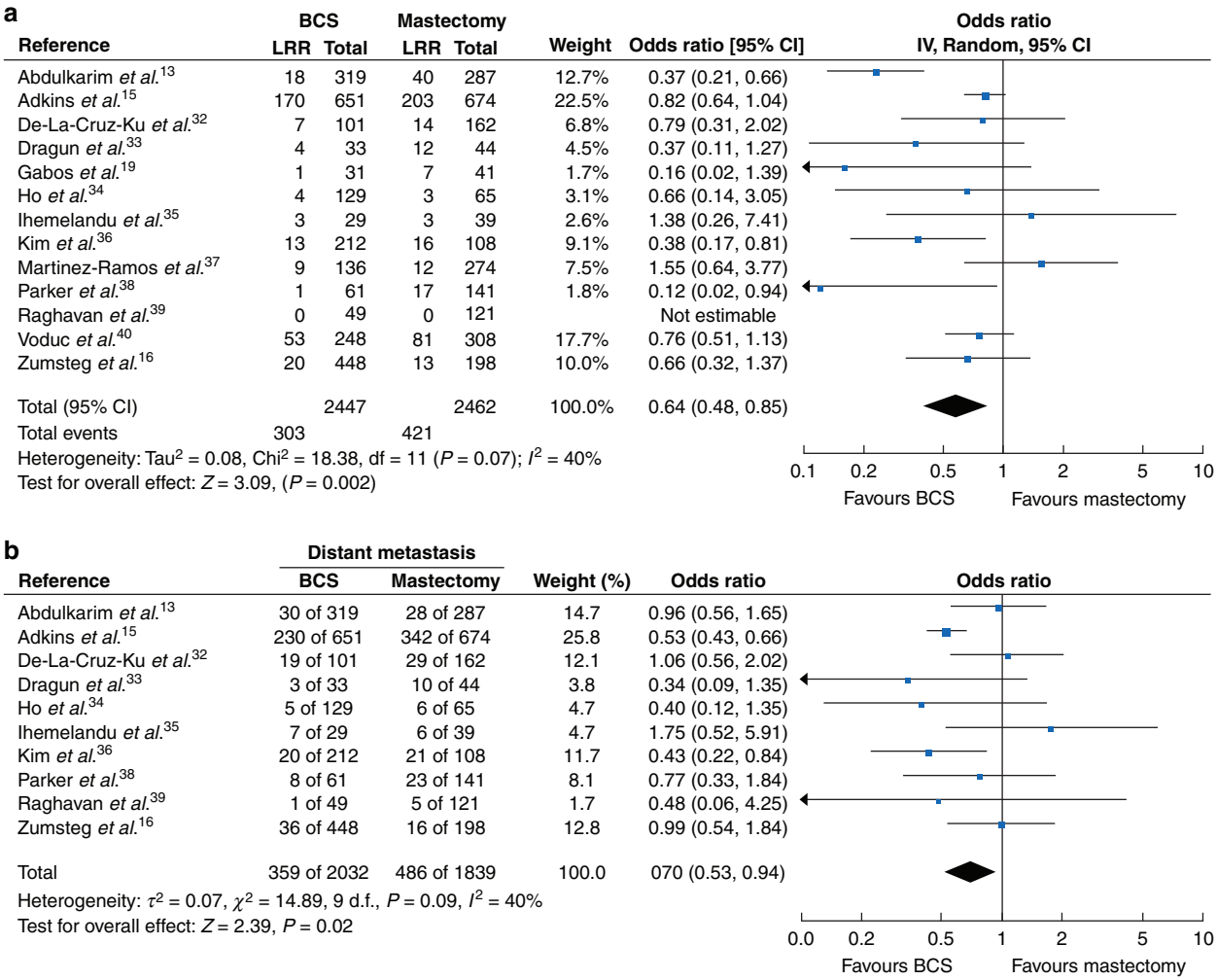

Fig. 2 Pooled odds ratios for locoregional recurrence and distant metastasis after breast-conserving surgery *versus* mastectomy

a Locoregional recurrence and **b** distant metastasis. An inverse-variance random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. BCS, breast-conserving surgery.

grade (6 studies), age (6 studies), nodal status (5 studies), and adjuvant chemotherapy (5 studies). In the present meta-analysis, the pooled HR of 0.78 (95 per cent c.i. 0.69 to 0.89; $P < 0.001$) indicated that the hazard for all-cause mortality among women undergoing BCS was significantly lower than that for women undergoing mastectomy (*Fig. 3*). Heterogeneity between study estimates was low ($I^2 = 20$ per cent). Of the study-level co-variables included in additional univariable adjustments (age, T1 tumours, positive axillary lymph nodes, tumour grade 1–2, adjuvant chemotherapy), none were statistically significant, and adjustment did not substantially change the pooled estimate (*Table 3*).

Discussion

The TNBC subtype is associated with shorter survival and increased early LRR and distant recurrences compared with non-TNBC subtypes[5,24,41]. Whether the locoregional treatment of TNBC influences long-term prognosis remains poorly understood. Pooled results from this meta-analysis found no evidence

Table 3 Unadjusted and adjusted pooled odds ratios for locoregional recurrence and distant metastasis, and hazard ratios for overall survival

	Co-variable	No. of studies	Pooled estimate (BCS *versus* mastectomy)	*P* for pooled estimate	β for co-variable (per 1 unit increase)	*P* for co-variable
Locoregional recurrence						
Unadjusted OR	–	12*	0.64 (0.48, 0.85)	0.002	–	–
Adjusted OR	Age (years)	9	0.56 (0.41, 0.77)	<0.001	-0.0503	0.27
	Follow-up (months)	11	0.58 (0.41, 0.84)	0.003	0.0035	0.52
	T1 (%)	11	0.64 (0.47, 0.88)	0.005	0.0051	0.63
	LVI (%)	8	0.63 (0.44, 0.90)	0.01	0.0113	0.49
	Radiotherapy (%)	9	0.49 (0.31, 0.78)	0.003	0.0247	0.47
Distant metastasis						
Unadjusted OR	–	10	0.70 (0.53, 0.94)	0.02	–	–
Adjusted OR	Age (years)	10	0.73 (0.60, 0.90)	0.003	0.0672	0.007
	Follow-up (months)	9	0.59 (0.50, 0.70)	<0.001	0.0175	0.006
	T1 (%)	9	0.73 (0.53, 1.01)	0.05	−0.0032	0.71
	LVI (%)	7	0.64 (0.45, 0.91)	0.01	−0.0081	0.56
	Radiotherapy (%)	8	0.64 (0.46, 0.88)	0.006	−0.0032	0.84
Overall survival						
Unadjusted HR	–	7	0.78 (0.69, 0.89)	<0.001	–	–
Adjusted HR	Age (years)	7	0.79 (0.69, 0.92)	0.002	−-0.116	0.40
	T1 (%)	7	0.82 (0.69, 0.97)	0.02	-0.0061	0.38
	N+ (%)	7	0.79 (0.70, 0.91)	<0.001	-0.0030	0.30
	Grade 1–2 (%)	7	0.75 (0.69, 0.83)	<0.001	-0.0140	0.12
	Adjuvant chemotherapy (%)	7	0.80 (0.67, 0.96)	0.02	-0.0029	0.61

Values in parentheses are 95 per cent confidence intervals. *A total of 13 studies reported locoregional recurrence, but for one study[39] there were no events in either treatment group; this study was not included in pooled analyses. BCS, breast-conserving surgery; LVI, lymphovascular invasion.

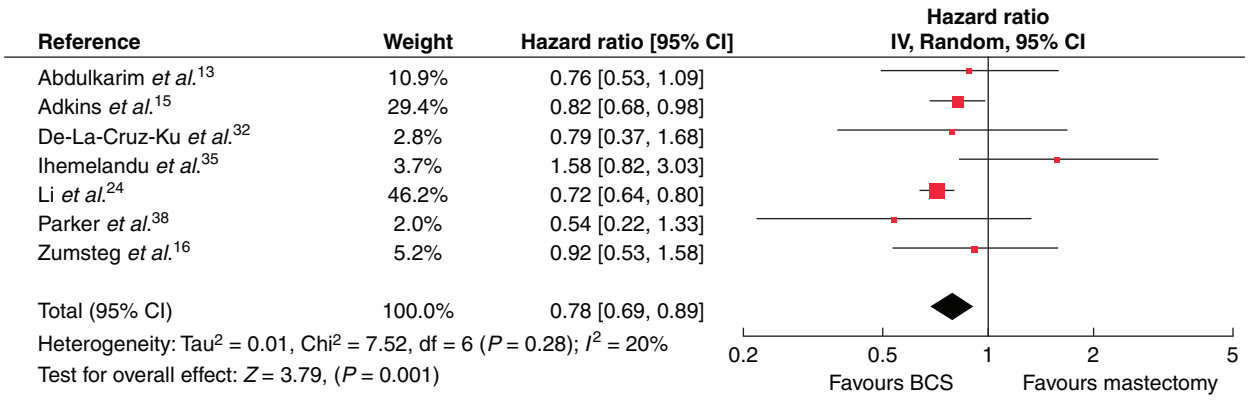

Fig. 3 Pooled hazard ratios for overall survival after breast-conserving surgery *versus* mastectomy

An inverse-variance random-effects model was used for meta-analysis. Hazard ratios are shown with 95 per cent confidence intervals. BCS, breast-conserving surgery.

of a detrimental effect of BCS compared with mastectomy on LRR, DM or OS in patients with TNBC.

A significantly lower odds of LRR among women undergoing BCS relative to those undergoing mastectomy was shown (OR 0.64, 95 per cent c.i. 0.48 to 0.85). LRR after locoregional treatment is a central issue in multimodal management of breast cancer, playing an important role in the decision-making process regarding surgical strategy. In a review of randomized trials published between 1995 and 2005, addressing the effects of RT and differences in extent of surgery, the Early Breast Cancer Trialists' Collaborative Group[42] demonstrated that local treatment comparison showed little (less than 10 per cent) absolute difference in the 5-year risk of local recurrence, although a subgroup analysis by breast cancer subtypes was not done. As many studies have reported that TNBC along with HER2-positive tumours exhibit a higher risk of LRR compared with luminal tumours[12,17,40,43,44], it has been argued that more radical surgery, such as mastectomy, would be a more appropriate treatment for TNBC[5,12,22]. Studies comparing the risk of LRR in patients with TNBC undergoing BCS or mastectomy have, however, reported conflicting results, reflected in the moderate statistical heterogeneity ($I^2 = 40$ per cent) observed here. The majority of studies (10 of 12) were consistent in the direction of effect, showing a reduced odds of LRR in BCS. The results of the present meta-analysis are broadly consistent with those of Wang and colleagues[21], who showed in a cohort of patients with TNBC that those who received BCS were less likely to develop LRR than those who underwent mastectomy. A limitation of that meta-analysis, encompassing publications up to 2013, was that several studies included only patients who underwent BCS.

The modelled estimates of this meta-analysis for DM showed that patients operated by BCS were less likely to develop DM than those having mastectomy (OR 0.70, 0.53 to 0.94). Differences between BCS and mastectomy, however, diminished with increasing age and follow-up time (*Table S2*). In a retrospective study, Dent and colleagues[7] observed a higher DM rate in patients with TNBC compared with other subtypes (33.9 *versus* 20.4 per cent; $P < 0.001$), and the mean time to DM in TNBC was less than that of other groups (2.6 *versus* 5.0 years; $P < 0.001$). Furthermore, it has been reported that DFS is more likely to be worsened by distant recurrence than by LRR, and this may affect OS[45].

A key endpoint of this meta-analysis was estimating survival outcomes in patients with TNBC who had BCS or mastectomy, as this knowledge gap has not been addressed in any meta-analysis to date. The pooled HR for OS showed a significantly lower hazard for all-cause mortality among women undergoing BCS relative to those undergoing mastectomy (HR 0.78, 0.69 to 0.89). Notably, there was less heterogeneity between studies for this outcome ($I^2 = 20$ per cent), likely owing to patient-level adjusted HR estimates. These survival outcomes are consistent with those of a recent study[46] investigating the effects of surgical treatment according to molecular subtypes in a cohort of 8656 young patients with breast cancer (aged 40 years or less). Even though patients with luminal subtypes had better prognosis than those with TNBC, women who had BCS experienced better OS and breast cancer specific-survival than those in the mastectomy group. Although the findings of the present meta-analysis likely also reflect selection of women with favourable prognosis for BCS, the modelled estimates provide reassurance that patients with TNBC selected for BCS do not have worse OS than those selected for mastectomy. The observed longer OS in patients who had BCS might be a consequence of reduced LRR and DM rates in this group, underscoring the negative impact of cancer recurrence on survival[17,42].

Although the modelled estimates for LRR, DM, and OS in the present meta-analysis indicate that BCS seems to be associated with a benefit over mastectomy, these results should be interpreted with caution because no randomized trials have been performed comparing BCS and mastectomy specifically for TNBC. Potential selection bias inherent in these non-randomized studies may have influenced the results. In general, the main message from the present findings is not to suggest that BCS is superior to mastectomy in TNBC, but rather that BCS is a viable option in suitable patients with TNBC.

There is no clear explanation for the observed lower risk of LRR and DM (and for longer OS estimates) among patients with TNBC who received BCS in the present meta-analysis. It can, however, be speculated that the reduced risk of LRR and DM in patients having BCS might partly be explained by an effect of postoperative RT as part of locoregional treatment. Many authors have reported that RT could benefit patients with TNBC after BCS compared with mastectomy[4,13,14,33]. Furthermore, RT might activate the immune system and provide effects beyond local control in breast cancer[4,47]. Evidence has been emerging on the immunomodulatory effects of RT, through induction of immunogenic cell death and subsequently increasing the sensitivity of lymphocytes to tumour cells[48]. Although more clinical studies are needed, recent research has shown that immunotherapy might be an ideal complement to RT in stimulating a systemic immune response to reject the tumour cells and inhibit DM[48–50]. Adjuvant RT was used in only a minority of patients undergoing mastectomy in this meta-analysis, and it was not possible to compare BCS with mastectomy + RT. Two studies that reported OS data for subgroups of patients receiving mastectomy + RT reported conflicting results; one[13] showed no difference in OS compared with BCS or mastectomy alone, whereas the other[24] showed significantly reduced OS, likely reflecting the selection of patients with poorer prognosis for mastectomy + RT.

The known paradigm in breast cancer management that BCS and mastectomy have equivalent long-term survival outcomes has been questioned in the setting of TNBC[4,13,37]. Evidence exists that BCS rates are higher in patients with luminal than non-luminal cancers, and that many patients with TNBC frequently undergo mastectomy, irrespective of tumour size[4,9,15,36]. Taking into account that generally about two-thirds of patients surgically treated for breast cancer receive BCS[22,51–53], the present data corroborate this finding, showing that 50.4 per cent of approximately 20 000 patients with TNBC underwent mastectomy. This concern partly prompted the present meta-analysis, the results of which should be considered within the context of current surgical practice, where it seems likely that mastectomy may more often be used among women who would otherwise be candidates for BCS[53–56].

Data on the use of preoperative chemotherapy were available in eight of 14 studies included in the meta-analysis, but it was actually used in only two studies[33,38]. Neoadjuvant chemotherapy is increasingly being used in patients with TNBC, with the aims of shrinking the tumour and facilitating breast conservation. The rates of pathological complete response depend largely on breast cancer subtype[9,57–59]. A recent meta-analysis[60] revealed that pooled rates of pathological complete response were 31.1 per cent in TNBC, more than observed among luminal tumours. The CALGB (Cancer and Leukemia Group B) 40603 randomized trial[9] documented a 42 per cent conversion rate from BCS-ineligible to -eligible among patients with stage II–III TNBC. Interestingly, in a cohort study[61] of 561 patients with breast cancer who had neoadjuvant chemotherapy, BCS did not impair DFS and OS compared with mastectomy, even though clinical T4 tumours and triple-negative disease were predictors of worse DFS. It is likely that the growing use of neoadjuvant chemotherapy will increase the number of patients with TNBC suitable for BCS in the near future.

This study has limitations mainly related to design and data shortcomings in the included source studies, such as retrospective design, heterogeneity in surgical populations and outcome definitions, and variation in patient inclusion criteria and selection for surgical treatment. Despite adjustment for co-variables in the modelled estimates, the results of meta-analysis regarding LRR and DM should be interpreted cautiously, as patients with smaller tumours were shown to be more likely to be selected for BCS than mastectomy. Some reports[13,19,62] have questioned tumour size as a critical determinant of clinical outcome and locoregional treatment in TNBC, given the propensity of this subtype to behave aggressively even when presenting clinically with small size and absence of nodal metastases.

In this large comparative analysis of patients with TNBC who had BCS or mastectomy, the pooled analyses showed that the risk of both LRR and DM in patients with TNBC who received BCS was lower than that in patients who underwent mastectomy, and the hazard of all-cause mortality was lower in patients who had BCS. Although these results should be interpreted with caution because of clinical selection for BCS or mastectomy in the studies analysed, the present data provide consistent evidence that women with TNBC who have BCS do not have a worse prognosis than those treated with mastectomy.

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Supplementary material

Supplementary material is available at *BJS* online.

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