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ORIGINAL PAPER

Extended adjuvant endocrine therapy in early breast cancer: a meta-analysis of published randomized trials

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Abstract Adjuvant endocrine therapy for 5 years is the standard adjuvant treatment for estrogen receptor-positive breast cancer while the benefits of extended adjuvant endocrine therapy (EAET) beyond 5 years are still controversial. That controversy prompted this meta-analysis to compare 5 years of adjuvant endocrine therapy only versus EAET. Eligible 11 randomized, controlled trials comprising 29,000 women were included. EAET showed no advantage in overall survival (OS) from all causes mortality (odds ratio [OR] = 0.98 (95% confidence interval [CI], 0.87–1.09); $P = 0.67$). On the other hand, compared with standard therapy, the pooled effects showed that EAET was associated with improvement in breast cancer-specific survival (OR = 0.87; 95% CI 0.79–0.96; $P = 0.004$), disease-free survival (DFS) (OR = 0.87; 95% CI 0.75–0.99; $P = 0.002$), disease recurrence (OR = 0.76; 95% CI 0.64–0.90; $P = 0.001$), and contralateral breast recurrence (OR = 0.74; 95% CI 0.59–0.93; $P = 0.008$). Improvement in DFS or disease recurrence was not shown in studies that compared 5 years of tamoxifen versus tamoxifen beyond 5 years. Subgroup analysis showed that EAET conferred more benefit for patients with positive lymph nodes. Rates of positive lymph nodes, the study size, and the median duration of follow-up were identified as variables that explained most of the demonstrated data heterogeneity. EAET should be considered as a preferred strategy for high-risk hormone-positive early breast cancer patients with positive lymph nodes; however, the benefit on OS could not be demonstrated.

Keywords Breast cancer · Endocrine therapy · Extended

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Introduction

The outcome of early breast cancer outcome has improved with better classification and characterization of the disease molecular biology [1], and the use of adjuvant systemic therapy including chemotherapy, endocrine therapy, and targeted agents for eligible patients [2–5].

Adjuvant endocrine therapy is the standard treatment for estrogen receptor-positive (ER+), early-stage breast cancer, which accounts for approximately 75% of all breast cancer [6]. According to the most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 20 trials ($n = 21{,}457$), 5 years of tamoxifen substantially reduced recurrence by 39% and breast cancer mortality by 30% [7]. On the other hand, clinical studies have shown that women with early-stage hormone-positive breast cancer—whose almost present two-thirds of all breast cancer patients—have a prolonged risk for recurrence, extending well beyond the 5 year from diagnosis where more than half of those recurrences happen after 5 years of adjuvant endocrine therapy [7, 8].

Earlier randomized clinical trial has consistently shown that extended adjuvant endocrine therapy (EAET) beyond 5 years for patients with hormone receptor- positive breast cancer can improve breast cancer outcome. That benefit was demonstrated in two recently published meta-analyses. The first meta-analysis examined the difference between 5 or more years of adjuvant endocrine therapy in 8 trials, including 29,138 patients [9]. The analysis concluded that EAET beyond 5 years of tamoxifen significantly improved overall survival (OS), breast cancer-specific survival (BCSS), and relapse-free survival (RFS) compared with 5 years of hormonal therapy only. That meta-analysis, however, included patients with unknown hormone receptor status (more than 6000 patients) in some of its analyses. Moreover, a demonstrated heterogeneity of the difference in RFS was not investigated.

The second meta-analysis included 5 trials comprising 21,554 patients and intended to examine the potential benefit of extending adjuvant tamoxifen beyond 5 years compared with adjuvant tamoxifen for 5 years only [10]. The analysis concluded that extended adjuvant tamoxifen is not associated with a significant reduction in recurrence, or a reduction in all-cause mortality; however, patients with lymph node positive breast cancer may achieve some benefit [10]. Similar to the first meta-analysis and despite a significant between-trials heterogeneity in the analysis of disease recurrence, the authors did not examine the potential variables that could explain such heterogeneity.

More recently, however, three trials presented at San Antonio Breast Cancer Symposium last December 2016 did not show similar benefit for EAET beyond 5 years [11–13]. The discrepancy in the outcome between earlier studies and the most recent ones has prompted this meta-analysis that included all EAET trials. We intended to explore the potential benefit of EAET only among those with known hormone receptor-positive tumors. Moreover, we also planned to examine any demonstrated heterogeneity.

Materials and methods

Search strategy

Between January 1996 and December 2016, we identified studies of interest by first conducting an electronic literature search of the following databases: MEDLINE, EMBASE, and the Cochrane Library. We also searched for relevant abstracts in conference proceedings of the American Society of Clinical Oncology, San Antonio Breast Conference, and the European Society for Medical Oncology.

We used Medical Subject Heading terms or Keywords: "breast OR mammary", "cancer OR neoplasm OR tumor OR carcinoma OR malignant", "hormone OR endocrine OR anti-hormone", "therapy OR treatment", "adjuvant", "tamoxifen OR letrozole OR exemestane OR anastrozole OR aromatase inhibitor (AI)", "clinical trial (mh) OR controlled clinical trial (mh) OR randomized controlled clinical trial [mh]", "comparative study (mh) OR prospective study (mh) OR evaluation study (mh) OR follow-up study [mh]". And the search terms were combined with the Keywords "extend OR extended OR extension OR prolonged OR prolongation".

Selection criteria

We included all studies that met the following criteria: (1) published in English language between January 1996 and December 2016; (2) included patients of any age and with hormone-positive non-metastatic breast cancer; (3) investigated the efficacy of EAET; (4) reported hazard ratio (HR), odds ratio (OR), or relative risk (RR) for disease-free survival (DFS), relapse-free survival (RFS), distant disease-free survival (DDFS), OS, BCSS, or contralateral breast cancer (CLBC) or reported adequate data allowing the OR to be computed; and (5) published as original articles or abstracts (no case reports, case series, reviews, comments, letters, or editorials). When two or more articles reported duplicate data, we included only the most recent data, the study with the longer follow-up, or the most relevant study. However, we included studies that have used the same data set but examined additional relevant outcomes.

Data extraction

Four authors (EI, MA, AB, AR) independently inspected each item identified by the search and applied the inclusion/exclusion criteria. All authors reviewed the articles and discussed the data intended for extraction.

We used a standardized Microsoft excel sheet to abstract data for each study that met inclusion criteria. Extracted data included the following fields: the study name, first author's last name, publication year, brief study description, study design, number of patients, median age, menopausal status, lymph nodes status, median follow-up, and outcome measures.

Outcome measures

The outcome measures extracted or computed were the ORs and its 95% confidence interval (CI) for outcome measures.

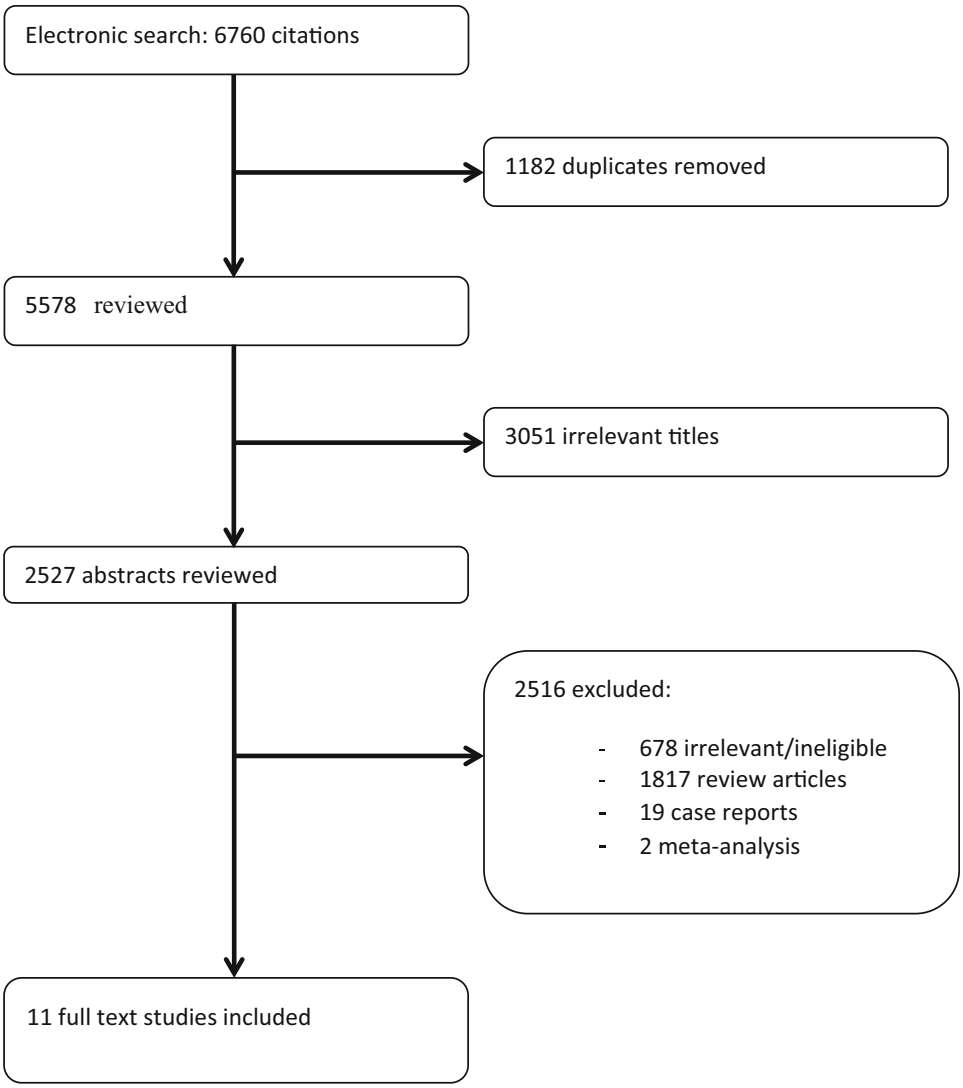

Fig. 1 Flowchart of literature search and the selection of the 11 included studies

Statistical analyses

The pooled estimates of the ORs and their CIs were the primary end points of the meta-analysis. We calculated unreported OR and its 95% CI using the procedure proposed by Tierney et al. [14] that is based on the method reported by Parmar et al. [15]. Where appropriate, we also used the built-in calculator of the Review Manager for Windows software version 5.2.3 to compute pertinent data (The Cochrane Collaboration, Oxford, UK). In studies that reported a univariate and a multivariate analysis for the same comparison, we only used the latter.

We assessed the heterogeneity of the results by inspecting the graphical presentations and by calculating a X^2 test of heterogeneity and the I^2 statistic of inconsistency [16, 17]. Statistically significant heterogeneity was defined as a X^2 P value less than 0.1 or an I^2 statistic greater than 50%. The pooled estimates of OR, together with the associated 95% CI, were obtained using the fixed-effects [18], or the DerSimonian and Laird random-effects model [19], where appropriate.

We performed meta-regression analysis to determine to what extent the effects of clinical variables could explain any demonstrated heterogeneity, i.e., trail size, classification groups, patients' median age, menopausal status, lymph node status, and median follow-up.

The dependent variable was the lnOR weighted for the inverse of variance to perform weighted least-square linear regression. We first conducted a univariate regression analysis for each relevant variable followed by a multivariate regression analysis including only variables found significant in the univariate analysis. In the meta-regression

Table 1 Patients and disease characteristics of the 11 included studies

Trial	Year	Description	Endpoints	No. EXP/CTR	Menopausal status, % (pre/post)		Median age (years)		Positive nodes (%)		Median follow-up (years)
					EXP	CTR	EXP	CTR	EXP	CTR	
Group I											
ECOG [24]	1996	Phase III, open-label, additional TAM indefinitely versus Obs (after TAM 5 y + CTX)	Disease recurrence or CLBC OS	73/67	57/43	53/47	NR	NR	100%	100%	5.6
SCOTTISH [23]	1996	Phase III, open-label, additional TAM indefinitely versus Obs (after TAM 5 y or at relapse)	Time to systemic recurrence BCSS OS	173/169	23/77	27/73	64	63	24.8%	20.7%	6.2
NSABP B-14 [25]	2001	Phase III, placebo-controlled, additional TAM 5 y versus placebo (after TAM 5 y)	DFS RFS OS	583/569	27/73	25/74	56	56	0	0	6.8
ATLAS [29]	2013	Phase III, open-label, additional TAM 5 y versus Obs (after TAM 5 y)	Disease recurrence or CLBC OS	3428/3418	8/90	8/90	51% < 55 y	51% < 55 y	NR	NR	7.6
ATTOM [30]	2013	Phase III, open-label additional TAM 5 y versus Obs (after TAM ≥ 4 y)	Disease recurrence including CLBC OS	3468/3485	NR	NR	NR	NR	31%	31%	4.2
Group II											
ABCSG Trial 6a [26]	2007	Phase III, open-label, additional ANA 3 y versus Obs (after TAM 5 y ± AG)	RFS (recurrence or CLBC) OS	387/469	0/100	0/100	67.8	68.5	34.1	31.1	5.2
MA.17 [27]	2008	Phase III, placebo-controlled, additional LT 5 y versus placebo ((after TAM 4.5–6 y + CTX (45%))	DFS (any recurrence and/or CLBC) DDFS CLBC OS	2583/2587	0/100	0/100	62.4	62	46%	46%	5.3
NSABP B-33 [28]	2008	Phase III, placebo-controlled, additional EXE 5 y versus placebo ((after TAM ~ 5 y + CTX (55%))	DFS (any recurrence, second breast cancer, or death without recurrence) OS RFS (recurrence or CLBC)	799/799	0/100	0/100	NR	NR	48%	48%	2.5
Group III											
DATA [13]	2016	Phase III, open-label, additional ANA 3 y versus Obs (after TAM 2–3 y + ANA 3 y)	DFS (any recurrence or CLBC) OS	827/833	0/100	0/100	NR	NR	67.8%	66.3%	4.1

Table 1 continued

Trial	Year	Description	Endpoints	No. EXP/CTR	Menopausal status, % (pre/post)		Median age (years)		Positive nodes (%)		Median follow-up (years)
					EXP	CTR	EXP	CTR	EXP	CTR	
LATER [31]	2016	Phase III, open-label, additional LT 5 y versus Obs (after ET ≥ 4 y)	Disease recurrence including CLBC	181/179	0/100	0/100	65	64	30.9%	36.3%	3.9
			DFS (recurrence, CLBC, or death)								
			OS								
NSABP B-42 [12]	2016	Phase III, placebo-controlled, additional LT 5 y versus placebo (after either AI 5 y or TAM ≤ 3 + AI to complete 5 y)	DFS (any recurrence, CLBC, or any death)	1959/1964	0/100	0/100	34% <60 y	35% <60 y	43%	42%	6.9
			BCFI								
			Distant recurrence								
			OS								

AG aminoglutethimide, *AI* aromatase inhibitor, *ANA* anastrozole, *BCSA* breast cancer-specific survival, *CLBC* contralateral breast cancer, *CTR* control arm, *CTX* chemotherapy, *DDFS* distant disease-free survival, *DFS* disease-free survival, *ET* endocrine therapy, *EXP* experimental arm, *LT* letrozole, *NR* not reported, *OS* overall survival, *Obs* observation, *RFS* relapse-free survival, *TAM* tamoxifen, *y* year

analyses, we assumed the data to be missing at random; therefore, observed study characteristics were used to impute missing data by means of multiple imputations [20].

We performed subgroup analyses to assess the potential contributions of various variables to the main outcome. We excluded studies that did not provide sufficient data to permit estimating relevant parameters in subgroup analyses. A funnel plot estimating the precision of trials (plots of logarithm of the OR against its inverse standard error) was examined for asymmetry to determine publication bias [21]. Publication bias was also quantified by the Begg and Mazumdar rank correlation method—Kendall's tau statistics with continuity correction—that examines the association between the effect estimates and their variances or their standard errors [22].

All statistical tests were two-sided. We used Comprehensive Meta-analysis (Biostat, version 3.3.070, Englewood New Jersey, USA) and Review Manager for all pooled estimates. For meta-regression analyses, we used Comprehensive Meta-analysis and the SPSS statistical package (IBM SPSS Statistics for Windows, version 20.0., New York, USA).

Results

We identified 6760 potentially relevant articles (Fig. 1). After exclusion of duplicate references, non-relevant literature, and those that did not satisfy the inclusion criteria, 11 candidate articles were included [12, 13, 23–31]. Notably, among the excluded studies were the MA.17R, IDEAL, and the Fédération Nationale des Centres de Lutte Contre le Cancer Breast Group trials. The MA.17R study was excluded because of its design, where 68.5% of eligible patients have received tamoxifen for 4.5–5.5 years and then 95.4% of patients have received 4.5–5.5 years of aromatase inhibitor; letrozole before randomization to an additional 5 years of letrozole versus placebo [32]. Therefore, the majority of patients in the placebo arm have already been exposed to an EAET.

In the IDEAL study, postmenopausal women with ER+ or progesterone-positive (PR+) early breast cancer patients were randomized to receive letrozole for longer (5 years) versus shorter period (2.5 years) after they had a 5-year of endocrine therapy (tamoxifen, AI, or tamoxifen followed by AI) [11]. Therefore, patients in both comparator arms received an EAET, albeit, for different duration.

The Fédération Nationale des Centres de Lutte Contre le Cancer Breast Group study was also excluded as the study compared patients randomized to suboptimal short-term tamoxifen (median 30 months) versus those receiving

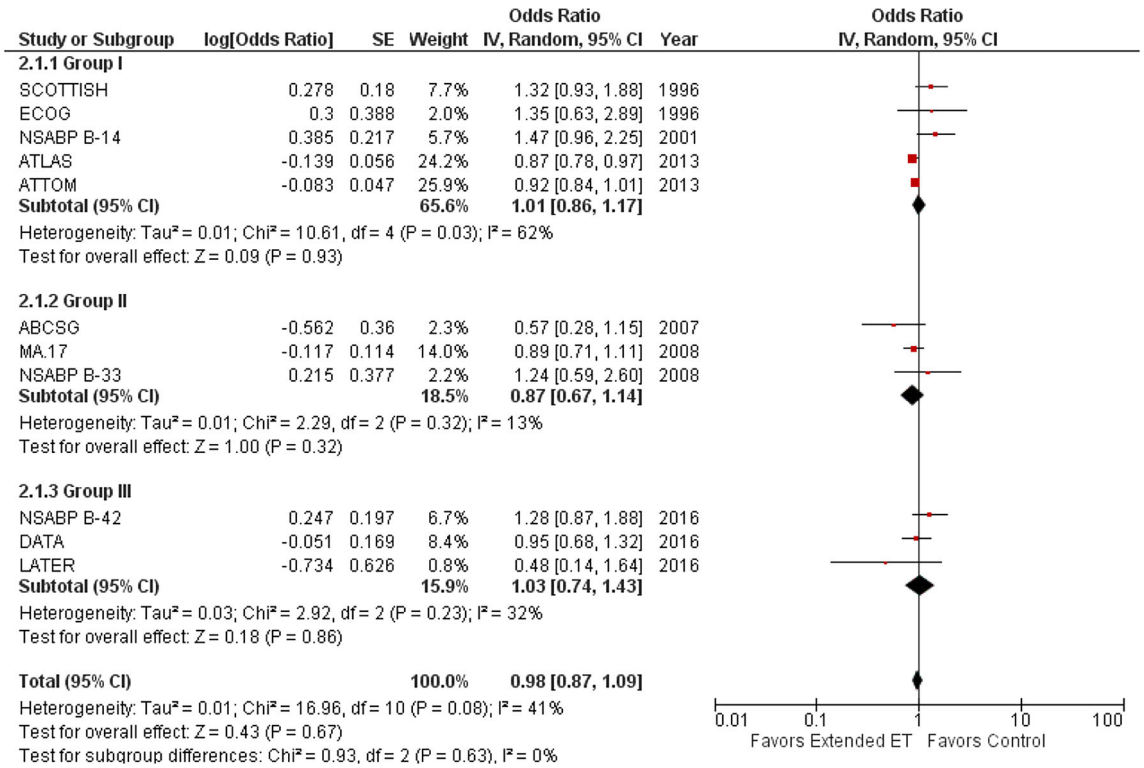

Fig. 2 Forest plot of the odds ratio (OR) of overall survival. *Squares* represent the OR of each single study (size of the *square* reflects the study-specific statistical weight); *horizontal lines* represent 95% confidence intervals; *diamonds* represent the pooled estimates, based on the random-effects model (heterogeneity testing: $I^2 = 0.41\%$; $P = 0.08$). ***ET***, endocrine therapy

Table 2 Summary of the outcome measures as reported from the included 11 studies

Trial	Overall survival OR (95% CI)	Breast cancer-specific survival OR (95% CI)	Disease-free survival OR (95% CI)	Relapse-free survival OR (95% CI)	Contralateral breast cancer OR (95% CI)
Group I					
ECOG [24]	1.35 (0.63, 2.89)	0.92 (0.33, 2.57)	0.54 (0.26, 1.12)	0.40 (0.18, 0.90)	
SCOTTISH [23]	1.32 [0.93, 1.88)	1.50 (0.96, 2.34)	1.44 (0.87, 2.38)	1.42 (0.82, 2.45)	
NSABP B-14 [25]	1.47 (0.96, 2.25)	–	1.34 (1.00, 1.79)	1.38 (0.87, 2.18)	0.82 (0.40, 1.69)
ATLAS [29]	0.87 (0.78, 0.97)	0.83 (0.72, 0.96)	0.91 (0.78, 1.06)	0.84 (0.76, 0.93)	0.76 (0.59, 0.98)
ATTOM [30]	0.92 (0.84, 1.01)	0.88 (0.77, 1.01)	0.95 (0.84, 1.08)	0.85 (0.76, 0.95)	0.93 (0.85, 1.02)
Group II					
ABCSG Trial 6a [26]	0.57 (0.28, 1.15)	0.57 (0.28, 1.15)		0.62 (0.40, 0.96)	0.67 (0.25, 1.80)
MA.17 [27]	0.89 (0.71, 1.11)		0.68 (0.56, 0.83)	0.63 (0.48, 0.82)	0.61 (0.39, 0.96)
NSABP B-33 [28]	1.24 (0.59, 2.60)	0.81 (0.33, 1.98)	0.70 (0.46, 1.06)	0.45 (0.25, 0.81)	
Group III					
DATA [13]	0.95 (0.68, 1.32)		0.78 (0.61, 1.00)		
LATER [31]	0.48 (0.14, 1.64)	0.14 (0.01, 2.75)	0.54 (0.27, 1.08)	0.11 (0.02, 0.53)	
NSABP B-42 [12]	1.28 (0.87, 1.88)		0.83 (0.70, 0.98)	0.69 (0.55, 0.87)	0.50 (0.32, 0.78)

CI confidence interval, *OR* odds ratio

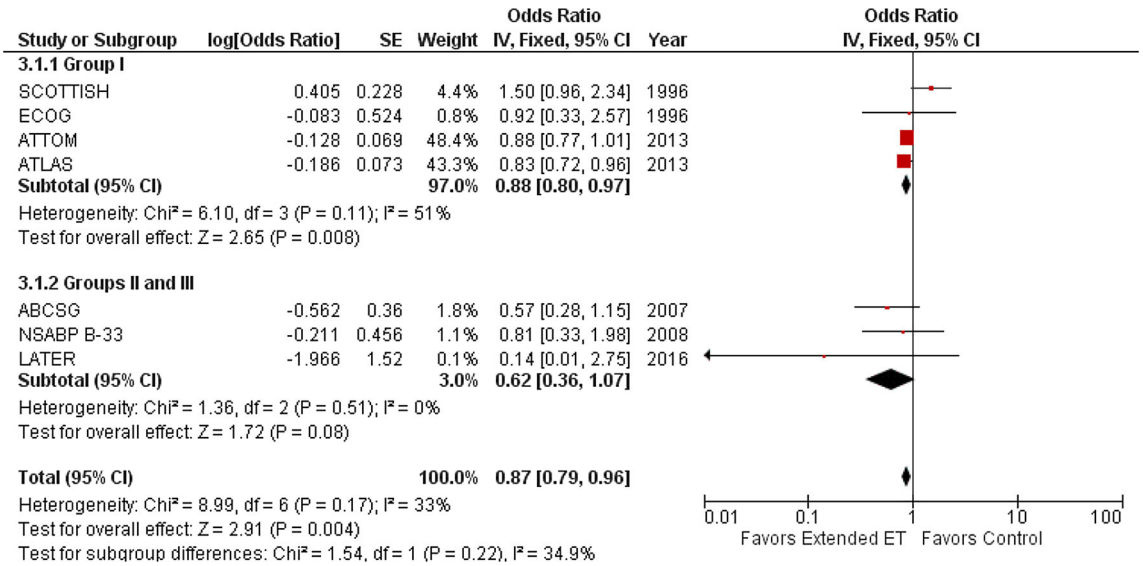

Fig. 3 Forest plot of the odds ratio (OR) of breast cancer-specific survival. *Squares* represent the OR of each single study (size of the *square* reflects the study-specific statistical weight); *horizontal lines* represent 95% confidence intervals; *diamonds* represent the pooled estimates, based on the fixed-effects model (heterogeneity testing: $I^2 = 0.33\%$; $P = 0.17$). *ET* endocrine therapy

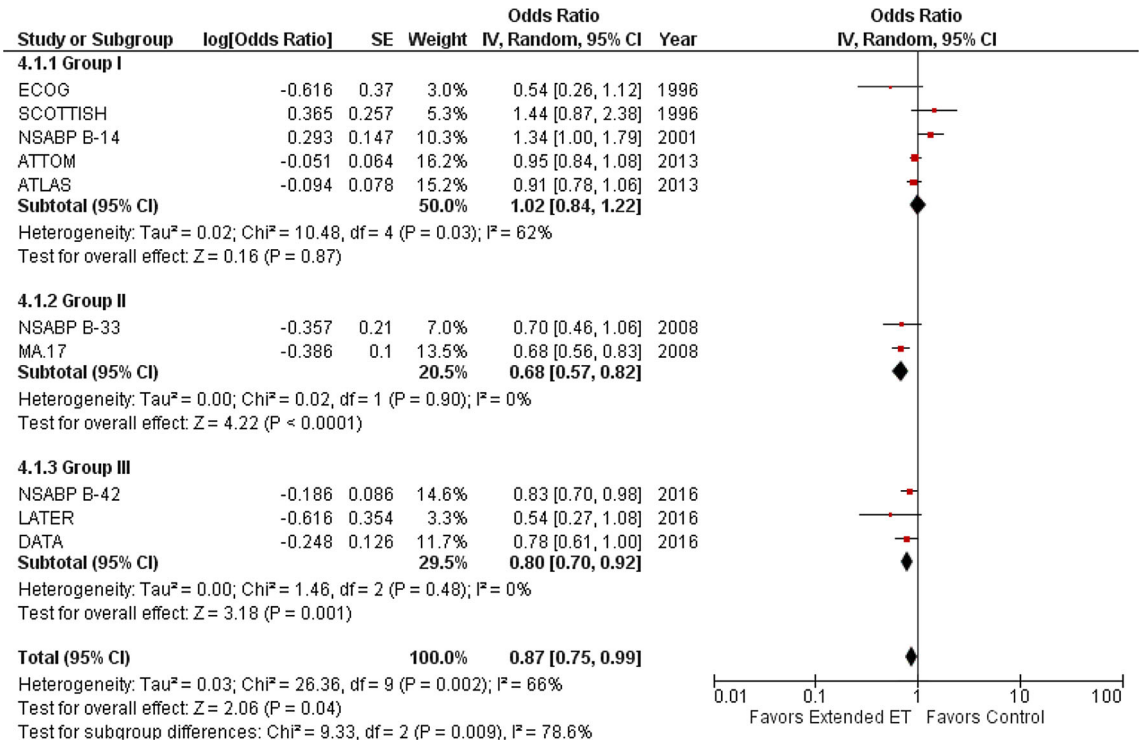

Fig. 4 Forest plot of the odds ratio (OR) of disease-free survival. *Squares* represent the OR of each single study (size of the *square* reflects the study-specific statistical weight); *horizontal lines* represent 95% confidence intervals; *diamonds* represent the pooled estimates, based on the random-effects model (heterogeneity testing: $I^2 = 0.66\%$; $P = 0.002$). *ET* endocrine therapy

Table 3 Meta-regression analyses

Model	Covariates	Standardized β coefficient	I^2 (%)	Adjusted R^2 (%)
Disease-free survival	Percentage of positive lymph nodes in EAET	−0.009	33.1	100
	Median follow-up duration	0.019		
Disease recurrence	Percentage of positive lymph nodes in EAET	−0.014	48.6	96
	Trial size	0.001		
Contralateral breast cancer	Percentage of positive lymph nodes in EAET	−0.012	0	100
	Trial size	0.001		

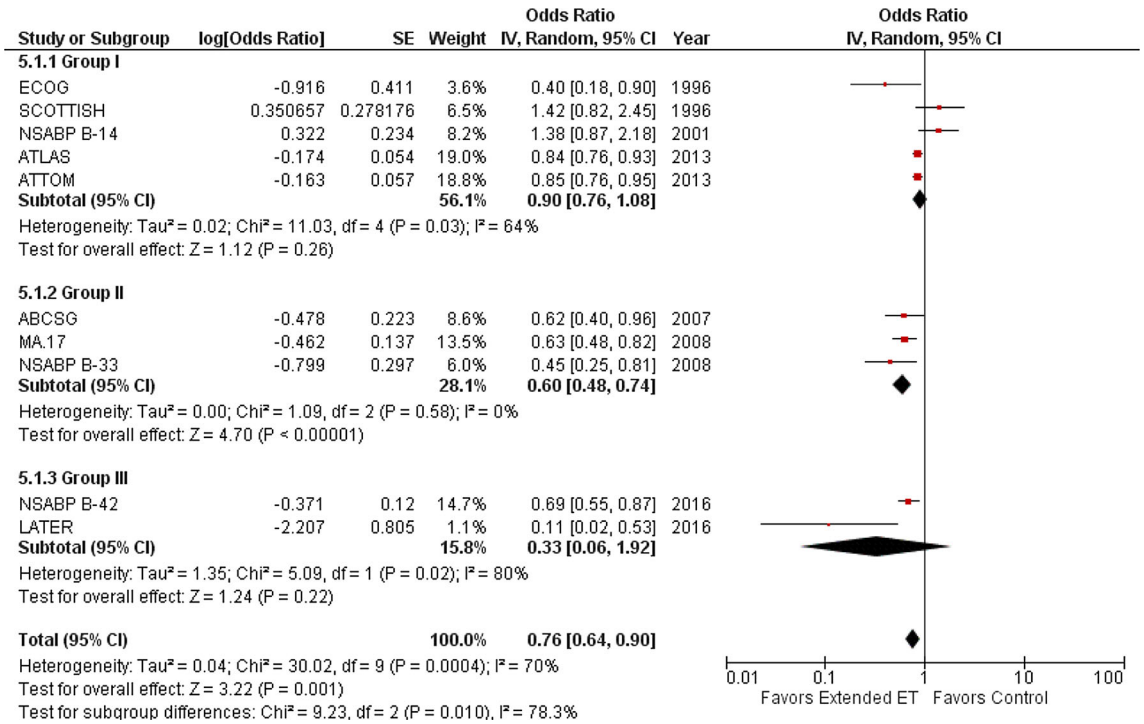

Fig. 5 Forest plot of the odds ratio (OR) of disease recurrence. *Squares* represent the OR of each single study (size of the *square* reflects the study-specific statistical weight); *horizontal lines* represent 95% confidence intervals; *diamonds* represent the pooled estimates, based on the random-effects model (heterogeneity testing: $I^2 = 0.70\%$; $P = 0.0004$). *ET* endocrine therapy

long-term tamoxifen (median 70 months). Therefore, patients in the experimental arm are considered as recipients of standard tamoxifen therapy duration [33].

Brief description of the included studies

Table 1 shows patients and disease characteristics of the 11 included studies. While Table 2 shows the main outcome measures of those studies. A total of 29,000 patients were included in this meta-analysis, and patients were nearly equally randomized between the EAET arms (14,461 patients) versus the control arms (14,539 patients). The median (95% CI) of the follow-up was 5.5 (3.9–6.9) years.

According to the initial endocrine therapy and the subsequent design, the 11 included studies were classified into three groups. Group I included 5 studies [23–25, 29, 30], where patients were randomized after 5 years of adjuvant tamoxifen, to receive either tamoxifen for an additional 5 years (7725 patients; 50%) versus observation or placebo (7708 patients; 50%). The total number of patients in this group was 14,433 patients (53% of the entire population included in this meta-analysis).

Group II included 3 studies [26–28], where 7624 patients (26% of this meta-analysis population) after an average of 5 years of adjuvant tamoxifen were randomized to receive AI for an additional 5 years (3769 patients; 49%) versus observation or placebo (3855 patients; 51%).

Group III included the remaining 3 studies [12, 13, 31], 5943 patients (21% of the entire meta-analysis population) after ≥4 years of various adjuvant endocrine therapy were randomized to receive anastrozole for 3 years or letrozole

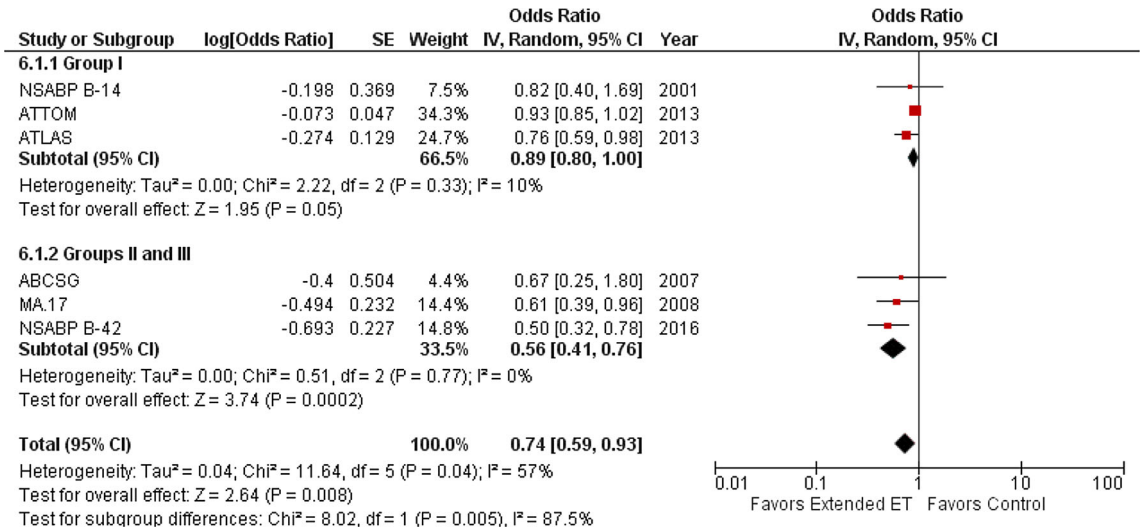

Fig. 6 Forest plot of the odds ratio (OR) of contralateral breast cancer. *Squares* represent the OR of each single study (size of the *square* reflects the study-specific statistical weight); *horizontal lines* represent 95% confidence intervals; *diamonds* represent the pooled estimates, based on the random-effects model (heterogeneity testing: $I^2 = 0.57\%$; $P = 0.04$). *ET* endocrine therapy

for 5 years (2967 patients; 50%) versus observation or placebo (2976; 50%).

Survival analysis

Meta-analysis of the OS from all causes mortality as shown in Fig. 2 (random effect model) demonstrated a pooled OR of 0.98 (95% CI, 0.87–1.09; $P = 0.67$) indicating lack of OS benefit of EATE. In none of the three groups an OS advantage was achieved. While there was shown heterogeneity in the model ($I^2 = 41\%$; $P = 0.08$), the meta-regression analysis failed to identify any variable that could explain such variability.

Analysis of BCSS was based on data derived from 8 out of the 11 studies (Fig. 3). The fixed-effects model showed that EATE was associated with 13% improvement in BCSS (OR = 0.87; 95% CI 0.79–0.96; $P = 0.004$). The model showed no heterogeneity ($I^2 = 33\%$; $P = 0.17$).

DFS

Fixed-effects analysis of the DFS (Fig. 4) showed model heterogeneity indicating that the data are not consistent with the assumptions of the fixed-effects model ($I^2 = 66\%$; $P = 0.002$). The random-effects model showed that EAET improved DFS by 13% (OR = 0.87; 95% CI 0.75–0.99; $P = 0.002$). On the other hand, that benefit was achieved in the studies assigned to Group II or Group III, while extending tamoxifen beyond 5 years had no favorable effect (group I).

To investigate potential heterogeneity within trials and between subgroups, a meta-regression analysis was performed. As shown in Table 3, increasing percentage of positive lymph nodes in the EAEA arms was inversely associated with the coefficient of the model, i.e., lower OR or larger benefit from EAET. On the other hand, longer median follow-up duration was positively associated with the coefficient of the model, i.e., larger OR or lower benefit from EAET. This model explained 100% of the heterogeneity in the DFS estimate ($R^2 = 1.0$).

Disease recurrence

Analysis of disease recurrence was based on data derived from 10 out of the 11 included studies (Fig. 5). The random-effects model demonstrated that EAET achieved a 24% improvement in the risk of disease recurrence (OR = 0.76; 95% CI 0.64–0.90; $P = 0.001$). However, that benefit was only shown in the pooled effect of studies in Group II, moreover, there was an overall model heterogeneity ($I^2 = 70\%$; $P = 0.0004$).

The meta-regression analysis showed that increasing percentage of positive lymph nodes in the EAEA arms was inversely associated with the coefficient of the model, i.e., lower OR or larger benefit from EAET (Table 3). On the other hand, the larger was the trial size the more positive was the coefficients of the model, i.e., larger OR or lower benefit from EAET. This model explained 96% of the heterogeneity in DFS estimate ($R^2 = 0.96$).

CLBC

Analysis of the risk of CLBC was based on data derived from 6 out of the 11 included studies (Fig. 6). The random-effects model demonstrated that EAET achieved a 26% reduction in the risk of CLBC (OR = 0.74; 95% CI 0.59–0.93; $P = 0.008$). There was no heterogeneity in the

Table 4 Subgroups analysis

Subgroups analysis	Included studies	Individual studies OR (95% CI)	Subgroups effects OR (95% CI)	Pooled effects OR (95% CI)
Recurrence versus median age				0.82 (0.75, 0.90)
<60 years	ABCSG [26]	0.60 (0.21, 1.72)	0.81 (0.70, 0.92)	
	NSABP B-33 [28]	0.27 (0.10, 0.73)		
		0.84 (0.72, 0.98)		
	ATLAS [29]	0.75 (0.52, 1.09)		
	DATA [13]			
≥60 years	ABCSG [26]	0.63 (0.39, 1.02)	0.84 (0.74, 0.95)	
	NSABP B-33 [28]	0.80 (0.48, 1.33)		
		0.86 (0.74, 1.00)		
	ATLAS [29]	0.85 (0.61, 1.19)		
	DATA [13]			
Recurrence versus receptors status				0.56 (0.36, 0.86)
ER+ and PR+	ABCSG [26]	0.32 (0.18, 0.57)	0.49 (0.35, 0.69)	
	NSABP B-33 [28]	0.40 (0.21, 0.78)		
		0.49 (0.36, 0.67)		
	MA.17 [27]	0.70 (0.53, 0.92)		
	DATA [13]			
ER+ and PR−	ABCSG [26]	3.49 (1.31, 9.30)	2.03 (0.72, 5.74)	
	MA.17 [27]	1.21 (0.47, 3.09)		
ER− and PR+	ABCSG [26]	0.97 (0.08, 11.51)	0.63 (0.20, 2.04)	
	MA.17 [27]	0.56 (0.15, 2.11)		
ER+ or PR+	NSABP B-33 [28]	0.52 (0.20, 1.35)	0.28 (0.10, 0.79)	
		0.18 (0.11, 0.30)		
	DATA [13]			
Recurrence versus nodal status				0.81 (0.68, 0.97)
Negative nodes	NSABP B-14 [25]	1.34 (1.00, 1.79)	0.96 (0.71, 1.29)	
		1.38 (0.87, 2.18)		
	ABCSG [26]	0.45 (0.27, 0.74)		
	MA.17 [27]	1.13 (0.55, 2.32)		
	NSABP B-33 [28]	0.85 (0.72, 1.01)		
		0.94 (0.59, 1.50)		
	ATLAS [29]			
	DATA [13]			
Positive nodes	ABCSG [26]	0.61 (0.34, 1.10)	0.70 (0.58, 0.84)	
	NSABP B-33 [28]	0.50 (0.30, 0.85)		
		0.61 (0.45, 0.83)		
	MA.17 [27]	0.83 (0.72, 0.96)		
	ATLAS [29]	0.72 (0.52, 1.00)		
	DATA [13]			
Recurrence site				0.87 (0.79, 0.97)
Local	ATLAS [29]	0.73 (0.54, 0.98)	0.82 (0.64, 1.05)	
	NSABP B-42 [12]	1.10 (0.68, 1.77)		

Table 4 continued

Subgroups analysis	Included studies	Individual studies OR (95% CI)	Subgroups effects OR (95% CI)	Pooled effects OR (95% CI)
Distant	ABCSG [26]	0.53 (0.29, 0.96)	0.89 (0.79, 0.99)	
	ATLAS [29]	0.91 (0.79, 1.05)		
	NSABP B-14 [25]	1.60 (0.81, 3.15)		
	NSABP B-42 [12]	0.69 (0.50, 0.96)		

CI confidence interval, *OR* odds ratio

effects size for trials in Group I or Groups II and III combined; however, the overall effects showed variability ($I^2 = 57\%$; $P = 0.04$).

The meta-regression analysis identified increased positivity of lymph nodes in experimental arms was associated with a larger benefit from EAET, while larger studies were linked to lesser benefit (Table 3).

Subgroups analyses

Several subgroups analyses were performed, however, only fewer number of studies reporting effects size in the subgroups (Table 4). Table 4 shows that the benefits of EAET in reducing recurrence were associated with tumors that are both ER+ and PR+, positive axillary lymph nodes, and reducing distant recurrence. On the other hand, the reduction in the risk of recurrence achieved with EAET was demonstrated regardless of patients' age.

Publication bias

Funnel plot and both Begg's and Egger's tests were performed to determine publication bias of the selected studies for OS and DFS analysis. The shapes of the funnel plots showed no evidence of clear asymmetry and quantitatively there was no publication bias [(OS: Begg's test $P = 0.81$ and Egger's test $P = 0.53$); (DFS: Begg's test $P = 0.28$ and Egger's test $P = 0.63$)].

Discussion

The current meta-analysis included 11 published randomized controlled studies comprising 29,000 patients, comparing two adjuvant hormonal therapy strategies for early disease hormonal positive breast cancer, i.e., EAET versus standard endocrine therapy of 5-year treatment. Our results demonstrated no OS benefit for EAET strategy among all treatment groups. However, there was DFS, BCSS, disease recurrence, and CLBC benefit, favoring EAET strategy.

In our analysis, we classified the studies into three groups. In group I, continuing tamoxifen for another 5 years showed no benefit across all the studies outcomes. This finding is consistent with the previous published meta-analysis by Al-Mubarak et al. [10]. In group II, the addition of 5 years of AI showed benefit in all the outcomes except for the OS. Similarly, in group III, where more AI treatment was given for another 3–5 years regardless of the first 5 years endocrine therapy strategy, there was clear benefit in all studied outcomes except for OS. The lack of OS benefit in the experimental arms in the current meta-analysis contrasts with the reported 11% reduction in all causes mortality (OR, 0.89; 95% CI 0.80–0.99; $P = 0.03$) in the meta-analysis of Petrelli et al. [9]. However, in the later analysis only 6 studies were included (15,635 patients) as compared with 11 studies (29,000 patients) in the present meta-analysis.

Decreasing recurrence rate using EAET was evident among patients with positive lymph nodes disease when compared to patients with negative lymph nodes. Moreover, the meta-regression analyses of DFS, disease recurrence, and CLBC showed that the percentage of positive lymph nodes partially explained between-trials heterogeneity. It may be prudent, therefore, to consider EAET for that group of patients. In support of this recommendation, it was shown in the most recent EBCTCG that among patients with ER+ patients with negative nodes and no chemotherapy administration, the 10-year recurrence rate was 19.1%, while the 10-year recurrence rate was 41.5% among those with positive lymph nodes [7, 34].

Interestingly, for disease recurrence EAET showed variable effect based on the ER or PR status. However, that conclusion was based on a subgroup analysis of data reported from 4 studies (Table 4). Nevertheless, the EBCTCG reported difference in the 10-year recurrence rates for ER+/PR+ , ER+/PR poor, and ER poor/PR+ of 24.8, 28.6, and 30.9%, respectively [7, 34].

In addition to the status of the lymph nodes, the meta-regression analyses identified median follow-up duration and trial size as potential variables that could partially explain heterogeneity in the effects size. Trial size and

timing of the analysis are strongly related to the assumption of the proportional hazards that most survival analysis methods are based [35]. Moreover, it was not surprising that studies with longer median follow-up duration showed less benefit from EAET. Recently, the International Breast Cancer Study Group analyzed 1808 patients with ER+ positive early breast cancer and it showed that the annual recurrence rates for the years 15–20 and 20–25 were 5.5 and 4.2%, respectively [36]. Moreover, the annual mortality rates for the same periods were also significant, i.e., 4.7 and 4.6%, respectively.

Based on our meta-analysis, we recommend EAET strategy for specific patients with positive lymph node disease regardless of their age. For postmenopausal women, we recommend the use of AI over tamoxifen as the agent of choice for EAET strategy. We also recommend further studies to assess the value of PR-negative status in guiding adjuvant treatment decisions for hormonal positive early breast cancer.

Compliance with ethical standards

Conflict of interest None.

Ethical standards The meta-analysis complies with the current laws of Saudi Arabia.

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