ORIGINAL ARTICLE

Optimal duration of endocrine therapy with extended aromatase inhibitors for postmenopausal patients with hormone receptor-positive breast cancer: a meta-analysis

Juan Chen[1] · Xiaohui Zhang[2] · Yan Lu[1] · Ting Zhang[1] · Zhaolian Ouyang[1] · Qiang Sun[2]

Abstract

Background The optimal duration of endocrine therapy for patients with hormone receptor-positive (HR-positive) breast cancer is still unclear. This meta-analysis aims to determine the optimal duration of endocrine therapy with extended aromatase inhibitors (AI) for postmenopausal patients with HR-positive early breast cancer who have finished 5 years of endocrine therapy.

Methods Eligible randomized controlled trials were classified into three categories according to the whole duration of endocrine therapy (10 years versus 5 years, 7–8 years versus 5 years, and 10 years versus 7–8 years). For each category, hazard ratio (HR) for disease-free survival (DFS) and overall survival (OS), and risk ratio (RR) for the incidence of adverse events were pooled.

Results Altogether 9 RCTs enrolling a total of 22,313 postmenopausal women with HR-positive breast cancer were included. Pooled data showed an improvement in DFS when extending endocrine therapy from 5 to 7–8 years (HR = 0.79 [0.69, 0.91]), specifically among those who had been treated with only tamoxifen (HR = 0.40 [0.22, 0.73]) or sequential tamoxifen followed by AI (HR = 0.82 [0.71, 0.95]), with tumors that were node-positive (HR = 0.72 [0.56, 0.93]), estrogen receptor (ER) and progesterone receptor (PR) positive (HR = 0.61 [0.47, 0.78]), or ≥ 2 cm in size (HR = 0.72 [0.51, 0.98]). However, no improvement in DFS was obtained when extending from 7–8 to 10 years (HR = 0.98 [0.87, 1.11]). In addition, the extension of endocrine therapy was not associated with an improvement in OS, but was associated with an increased risk of bone fracture and osteopenia/osteoporosis.

Conclusion Patients who have been treated with AI for 5 years, with tumors that are node-negative, ER+/PR− or ER−/PR+, and < 2 cm in size do not need to receive extended AI therapy. For those who have been treated with only tamoxifen or sequential tamoxifen followed by an AI for a total of 5 years, with tumors that are node-positive, ER+/PR+ or ≥ 2 cm in size, 2–3 years of extended AI is necessary and maybe enough.

Juan Chen and Xiaohui Zhang are the co-first authors contributed equally to this work

Zhaolian Ouyang and Qiang Sun contributed equally to this work

✉ Zhaolian Ouyang
  ouyangzhaolian8888@163.com

✉ Qiang Sun
  sunqpumch@163.com

Extended author information available on the last page of the article

Introduction

Breast cancer is the malignant tumor with the highest incidence among women. Studies have note that about 70% of breast cancers are estrogen receptor (ER) or progesterone receptor (PR) positive [1]. Endocrine therapy is the main choice for these patients to reduce recurrence and mortality [2].

In the 1970s, the clinical application of tamoxifen became a milestone in breast cancer endocrine therapy, which had been considered the optimal choice for patients with hormone receptor-positive (HR-positive) breast cancer for a

long time [3]. In the 1990s, the advent of the third generation aromatase inhibitors (AI) brought breast cancer endocrine therapy into a new era. Clinical studies including ATAC, BIG 1–98, ABCSG-8 and ITA and the EBCTCG meta-analysis have proven the superiority of 5-year AI-containing therapies over 5-year tamoxifen among postmenopausal patients with HR-positive early breast cancer [4–8]. Consequently, international guidelines recommended the use of AI or sequential tamoxifen followed by an AI for a total of 5 years in postmenopausal patients with HR-positive early breast cancer [3].

Despite the success of 5-year adjuvant endocrine therapy, it is reported that women with HR-positive breast cancer have a prolonged risk of recurrence, which means that recurrences can still occur after 5-year adjuvant endocrine therapy. In recent years, many clinical trials have evaluated the efficacy of extended endocrine therapy and have drawn inconsistent conclusions. With extended endocrine therapy, improved disease-free survival (DFS) was demonstrated in studies including AERAS, MA17, GIM4 LEAD, but was not demonstrated in NSABP B-42, NSABP B-33, DATA, ABCSG-16 and IDEAL [9–17]. In the above-mentioned studies, the whole duration of endocrine therapy was not the same, with some extending from 5 to 7–8 years, and the others extending from 5 to 10 years.

The duration of adjuvant endocrine therapy for breast cancer is one of the hot topics in recent years. Although a previous meta-analysis published in 2020 have indicated the potential benefit of endocrine therapy with extended AI [18], there is no meta-analysis focusing on the optimal duration of endocrine therapy so far. Considering the economic burden, psychological burden, and side effects of extended therapy, the optimal duration of and the potential population who can benefit from endocrine therapy with extended AI are still under discussion [19, 20].

Here we will report a meta-analysis of randomized controlled trials (RCT) to explore the optimal duration of endocrine therapy with extended AI for postmenopausal patients with HR-positive early breast cancer who have finished 5 years of endocrine therapy.

Materials and methods

Literature search

On March 9, 2020, RCTs were searched in PubMed, EMBASE and Cochrane databases using the terms "aromatase inhibitor* OR aromatase inhibiting OR aromatase inhibitor OR anastrozole OR exemestane OR letrozole", "extended OR prolonged OR continued OR duration", "postmenopausal OR post-menopausal or post-menopause", "breast neoplasm OR breast cancer" and "trial OR study". In addition, RCTs were also searched among conference papers of the San Antonio Breast Cancer Symposium (SABCS) and the American Society of Clinical Oncology (ASCO). For studies no enough data were reported in published articles, the study authors were contacted.

Inclusion and exclusion criteria

Studies meeting all of the following criteria were included: (1) RCTs without obvious bias; (2) conducted among postmenopausal patients with HR-positive early breast cancer; (3) investigating the efficacy and safety of endocrine therapy with extended AI; (4) enrolling patients who have received prior endocrine therapy including tamoxifen, AI, or tamoxifen followed by AI; (5) can provide data comparing endocrine therapies administrated for a total of 10 years versus 5 years, 7–8 years versus 5 years, or 10 years versus 7–8 years. There were no restrictions on publication dates or languages.

Studies meeting any of the following criteria were excluded: (1) reviews, meta-analyses, letters, editorials, and animal experiments; (2) with obvious bias; (3) the extended therapies were not AI; (4) the duration of prior endocrine therapy had been much longer than 5 years.

Literature screening and data extraction

Articles retrieved from different sources were pooled and duplicates were removed. Then the titles and abstracts of all articles were reviewed, and those not meeting the inclusion criteria were removed. For articles that cannot be judged through titles and abstracts, full texts were reviewed.

For studies that were judged to have meet all the inclusion criteria, the following information were extracted: study code, study design, patient population, treatment before randomization, treatment after randomization, total duration of endocrine therapy, number of patients, median age, median follow-up, DFS, overall survival (OS), and adverse events.

The above-mentioned processes were conducted by two researchers independently. Disagreements were resolved through discussion or were referred to a third person.

Quality assessment

The Cochrane risk of bias tool embedded in Review Manager 5.2 was used to assess the risk of bias for included studies. For each study, low risk, unclear risk or high risk of bias was assigned to each domain of the tool, including selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential bias.

Statistical analysis

This study was designed to explore the optimal duration of endocrine therapy with extended AI for postmenopausal patients with HR-positive early breast cancer who have finished 5 years of endocrine therapy (including tamoxifen, AI, or tamoxifen followed by AI). According to whole duration of endocrine therapy (the duration of prior endocrine therapy plus that of extended AI), all RCTs were classified into three categories: (1) comparing 10 years versus 5 years of endocrine therapy; (2) comparing 7–8 years versus 5 years of endocrine therapy; (3) comparing 10 years versus 7–8 years of endocrine therapy.

DFS was the endpoint of special interest in the study, and OS and the incidence of adverse events were evaluated as well. Pooled HR along with 95% confidence interval (CI) were calculated for DFS and OS. Pooled risk ratio (RR) along with 95% CI were calculated for the incidence of adverse events. In addition, subgroup analyses were performed for DFS based on the following stratification factors: the type of prior 5 years of endocrine therapy (5 years of tamoxifen, 5 years of AI, or 2–3 years of tamoxifen followed by 3–2 years of AI), node status (negative, positive), hormone receptors status (estrogen receptor [ER] positive and progesterone receptor [PR] positive, ER or PR positive) and tumor size (<2 cm, ≥ 2 cm). The heterogeneity were evaluated by I^2. The fixed-effect model would be used if $I^2 \leq 50\%$, and the random-effect model would be used if $I^2 > 50\%$. All statistical analysis were conducted in Stata 15. All tests were 2-tailed, and $P < 0.05$ was considered as statistically significant.

Results

Altogether 1051 records were identified through searching in Pubmed, EMBASE and Cochrane Library, or from ASCO or SABCS conference papers. In addition, four additional records were obtained by contacting study authors. After removing the duplicates, 596 records were screened with titles and abstracts, among which 532 were excluded because of title or abstract not relevant. The remaining 64 records were assessed with full texts, among which 32 were excluded because of ineligibility: 8 records were not RCTs; 20 records did not investigate the safety and efficacy of extended AI therapy; 1 record cannot provide data comparing endocrine therapies administrated for 10 years versus 5 years, 7–8 years versus 5 years, or 10 years versus 7–8 years because of its intermittent extension design (the SOLE study) [21]; 1 record has obvious bias because of enrolling a larger proportion of patients with node-positive, >2 cm tumors in the observation group as compared to the letrozole group (the LATER study) [22]; two records were related to one study

in which patients had received 10 years of endocrine therapy before randomization (the MA 17R study) [23]. As to the remaining 32 articles, the results of 9 RCTs were reported, with some RCTs having been reported in more than 1 publications because of subgroup analysis or updated analysis. The PRISMA flow diagram is shown in Fig. 1.

The included studies were summarized in Table 1, and the risk of bias for included studies were shown in Fig. 2 [10–17, 24]. According to the total duration of endocrine therapy, the nine RCTs were classified into three categories as follows: (1) 10 years versus 5 years of endocrine therapy, including AERAS, MA17, NSABP B-42 and NSABP B-33; (2) 7–8 years versus 5 years of endocrine therapy, including ABCSG 6a, DATA and GIM4 LEAD; (3) 10 years versus 7–8 years of endocrine therapy, including ABCSG-16 and IDEAL.

Disease-free survival (DFS)

All 9 RCTs enrolling a total of 22,313 postmenopausal women with HR-positive breast cancer were available for the analysis of DFS. Figure 3 shows the forest plot of HR for DFS. Pooled data showed that extending endocrine therapy can improve DFS as compared to shorter treatment duration (HR $= 0.77$ [0.68, 0.89]; $I^2 = 66.4\%$, random effects model), especially when extending from 5 to 10 years (HR $= 0.67$ [0.52, 0.85]; $I^2 = 68.7\%$, random effects model) and from 5 to 7–8 years (HR $= 0.79$ [0.69, 0.91]; $I^2 = 0.0\%$, fixed effects model). However, statistical data shown that extending endocrine therapy from 7–8 to 10 years cannot significantly improve DFS (HR $= 0.98$ [0.87, 1.11]; $I^2 = 0.0\%$, fixed effects model).

Subgroups analyses of DFS

Table 2 shows the HR for DFS stratified by initial 5 years of therapy (5 years of tamoxifen, 5 years of AI, or 2–3 years of tamoxifen followed by 3–2 years of AI), node status (negative, positive), hormone receptors status (ER+ and PR+, ER+ or PR+) and tumor size (0–2 cm, ≥ 2 cm).

When extending endocrine therapy from 5 to 10 years, the benefit of extended AI in reducing recurrence could be observed in patients who had been treated only with previous 5 years of tamoxifen (HR $= 0.61$ [0.49, 0.76]) or 2–3 years of tamoxifen followed by 3–2 years of AI (HR $= 0.74$ [0.57, 0.97]), with tumors that were node-positive (HR $= 0.63$ [0.48, 0.83]), ER + /PR + (HR $= 0.5$ [0.42, 0.71]), or ≥ 2 cm in size (HR $= 0.51$ [0.35, 0.75]), but could not be observed in those who had received 5 years of AI, with tumors that were node-negative, ER+/PR− or ER−/PR+, and <2 cm in size.

When extending endocrine therapy from 5 to 7–8 years, the benefits of extended AI in reducing recurrence could be observed in patients who had been treated only with previous

Fig. 1 The PRISMA flow diagram showing the process of identifying eligible randomized controlled trials. *ASCO* the American Society of Clinical Oncology, *SABCS* the San Antonio Breast Cancer Symposium, *RCT* randomized controlled trial, *AI* aromatase inhibitor
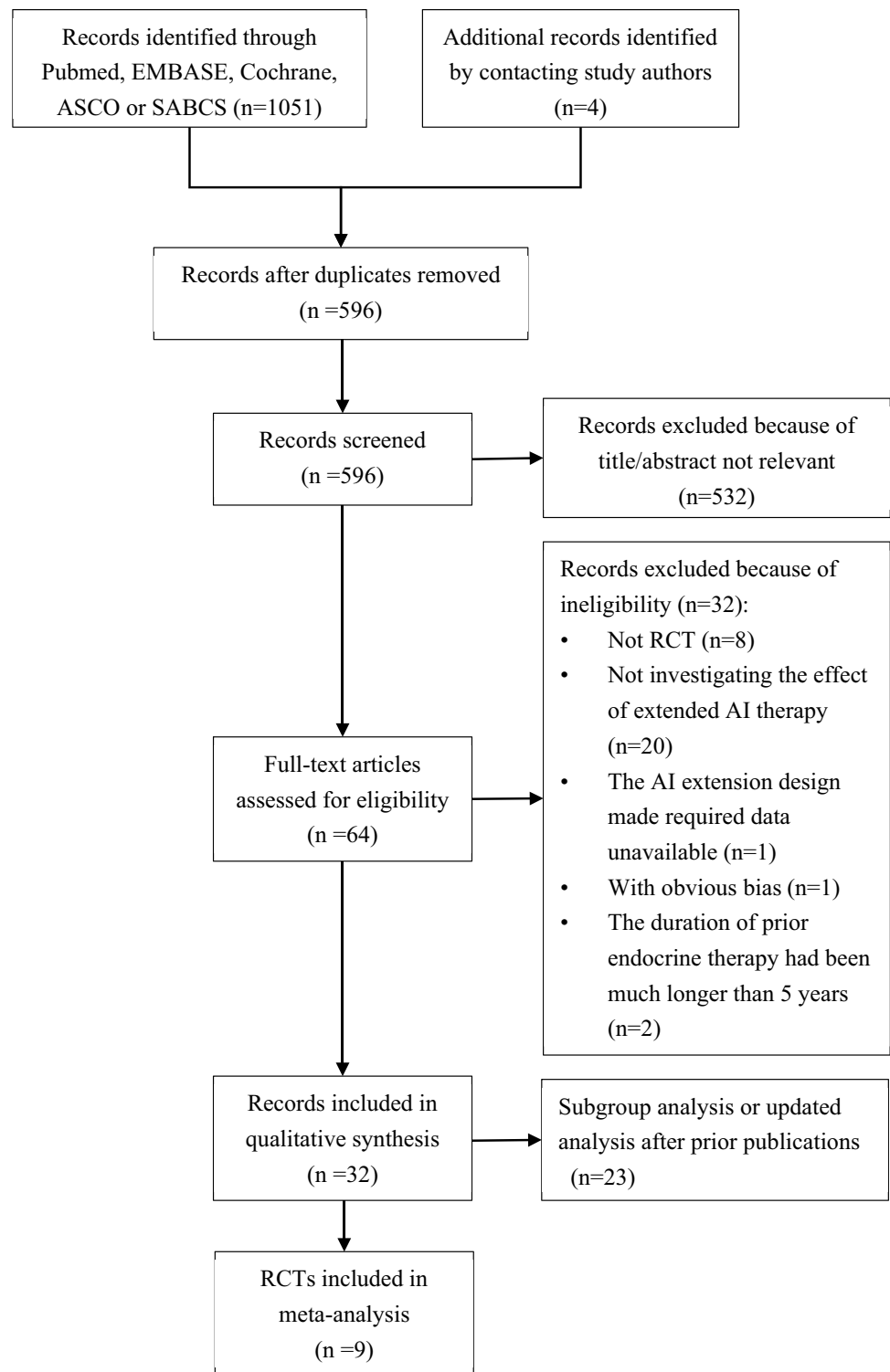
5 years of tamoxifen (HR = 0.40 [0.22, 0.73]) or 2–3 years of tamoxifen followed by 3–2 years of AI (HR = 0.82 [0.71, 0.95]), with tumors that were node-positive (HR = 0.72 [0.56, 0.93]), ER+/PR+ (HR = 0.61 [0.47, 0.78]), or ≥ 2 cm in size (HR = 0.72 [0.51,0.98]), but could not be observed in

those who had received 5 years of AI, with tumors that were node-negative, ER+/PR− or ER−/PR+, and < 2 cm in size.

When extending endocrine therapy from 7–8 to 10 years, no statistically significant benefit of extended AI in reducing recurrence can be observed in the whole population or in any

Table 1 Main characteristics of studies included in this meta-analysis

Study	Design	Patients description	Treatment before randomization	Treatment after randomization (study vs. control)	Total duration of endocrine therapy (study vs. control)	No. of patients	Median age (years)	Median follow-up
ABCSG-16	A prospective, randomized, multicenter, phase 3 study	Postmenopausal women with stage I–III HR-positive early breast cancer who were recurrence-free after 5 years of therapy with Tam or AI or TAM+AI	5 Y Tam, 5 Y AI or 5 Y Tam+AI	5 Y ANA vs. 2 Y ANA	10 Y vs. 7–8 Y	3469	64	106.2 M
ABCSG 6a	A randomized, open-label study	Postmenopausal women with endocrine-responsive, primary unilateral stage I–II breast cancer who were recurrence-free after 5 years of adjuvant therapy with Tam or Tam+aminoglutethimide in ABCSG Trial 6	5 Y Tam or 5 Y Tam+aminoglutethimide	3 Y ANA vs. no treatment	7–8 Y vs. 5 Y	856	68.1	62.3 M
AERAS	A prospective, randomized, open-label, multicenter, phase 3 study	Postmenopausal patients with stage I–III HR-positive breast cancer who were disease-free after 5 years of ANA or Tam 2–3 years followed by ANA 3–2 years	5 Y ANA or 5 Y Tam+ANA	5 Y ANA vs. no treatment	10 Y vs. 5 Y	1697	64.3 vs. 64.5	4.9 Y
DATA	A prospective, randomized, open-label, multicenter, phase 3 study	Postmenopausal women with HR-positive early breast cancer who were recurrence-free after 2–3 years of adjuvant Tam therapy	2–3 Y Tam	6 Y ANA vs. 3 Y ANA	7–8 Y vs. 5 Y	1660	57.7 vs. 57.6	4.2 Y

Table 1 (continued)

Study	Design	Patients description	Treatment before randomization	Treatment after randomization (study vs. control)	Total duration of endocrine therapy (study vs. control)	No. of patients	Median age (years)	Median follow-up
GIM4 LEAD	A prospective, randomized, multicenter study	Postmenopausal patients with HR-positive early breast cancer who were free of recurrence after 2–3 years of Tam therapy	2–3 Y Tam	5 Y LET vs 2–3 Y LET	7–8 Y vs. 5 Y	2056	61 vs. 60	10 Y
IDEAL	A randomized, open-label, multicenter, phase 3 study	Postmenopausal women with HR-positive early breast cancer who had completed five years of any adjuvant endocrine therapy	5 Y Tam, 5 Y AI or 5 Y Tam+AI	5 Y LET vs. 2.5 Y LET	10 Y vs. 7–8 Y	1824	NR	6.6 Y
MA17	A randomized, double-blind, placebo-controlled, phase 3 study	Postmenopausal women with HR-positive primary breast cancer who had completed five years of adjuvant Tam therapy	5 Y Tam	5 Y LET vs. placebo	10 Y vs. 5 Y	5187	62	30 M
NSABP B-33	A randomized, double-blind, placebo-controlled study	Postmenopausal patients with clinical $T_{1-3}N_{0-1}M_0$ HR-positive invasive breast cancer who were disease free after 5 years of Tam therapy	5 Y Tam	5 Y exemestane vs. 5 Y placebo	10 Y vs. 5 Y	1598	NR	30 M
NSABP B-42	A randomized, double-blind, placebo-controlled, phase 3 study	Postmenopausal women with stage I–IIIA HR-positive breast cancer who were disease-free after 5 years of therapy with AI or Tam+AI	5 Y AI or 5 Y Tam+AI	5 Y LET vs. 5 Y placebo	10 Y vs. 5 Y	3966	NR	6.9 Y

HR hormone-receptor, *Tam* tamoxifen, *AI* aromatase inhibitor, *ANA* anastrozole, *LET* letrozole, *Y* years, *M* months

Fig. 2 Quality of studies included in the meta-analysis

from 5 to 10 years (HR = 1.05 [0.87, 1.27]; I^2 = 20.4%, fixed effects model), from 5 to 7–8 years (HR = 0.90 [0.69, 1.17]; I^2 = 0.0%, fixed effects model) or from 7–8 to 10 years (HR = 1.02 [0.86, 1.20]; I^2 = 0.0%, fixed effects model).

Adverse events (AE)

All 9 RCTs have reported adverse events. Table 3 summarizes the most commonly reported adverse events reported in these studies. According to our analysis, the extension of adjuvant endocrine therapy from 5 to 10 years was associated with an increased risk of bone fracture (RR = 1.27 [1.05, 1.54]), osteopenia/osteoporosis (RR = 1.24 [1.10, 1.40]), bone pain (including arthralgia) (RR = 1.28 [1.11, 1.49]), joint stiffness (RR = 2.40 [1.68, 3.43]), myalgia (RR = 1.24 [1.10, 1.39]) and alopecia (RR = 1.42 [1.09, 1.85]). The extension of adjuvant endocrine therapy from 5 years to 7–8 years was associated with an increased risk of bone fracture (RR = 1.36 [1.01, 1.84]), osteopenia/osteoporosis (RR = 1.73 [1.22, 2.45]) and bone pain (including arthralgia) (RR = 1.34 [1.03, 1.73]). The extension of adjuvant endocrine therapy from 7–8 to 10 years was associated with an increased risk of bone fracture (RR = 1.57 [1.22, 2.02]) and osteopenia/osteoporosis (RR = 1.70 [1.28, 2.26]).

Discussion

Before 2010, patients with HR-positive breast cancer were generally recommended to receive endocrine therapy for five years. However, in recent years, studies have shown that HR-positive breast cancer has two peaks of recurrence during 2–3 years and 7–8 years after surgery, with more than 50% of recurrences occurring after discontinuing 5 years of adjuvant endocrine therapy [25, 26]. Therefore, the benefits and risks of extended adjuvant endocrine therapy has become a hot topic in this field. In recent years, the results of clinical studies on extended adjuvant endocrine therapy have been disclosed gradually. Studies including AERAS, MA17, GIM4 LEAD and ABCGS 6a shown that extended AI therapy can reduce recurrences, while studies such as NSABP B-42, NSABP B-33, DATA, ABCSG-16 and IDEAL failed to support this point [10–17, 24]. In the above-mentioned studies, the whole duration of endocrine therapy was not the same, with some extended to 7–8 years, and the others extended to 10 years. Our study is the first meta-analysis focusing on the optimal duration of endocrine therapy.

According to the results of DFS in this meta-analysis, extending endocrine therapy from 5 to 7–8 years or to 10 years could reduce disease recurrence significantly. To be more specifically, according to data presented in previous studies, distant recurrence (HR for 10 years vs 5 years: 0.51 [0.32, 0.84], 0.60 [0.43, 0.84] and 0.72 [0.53, 0.97] reported
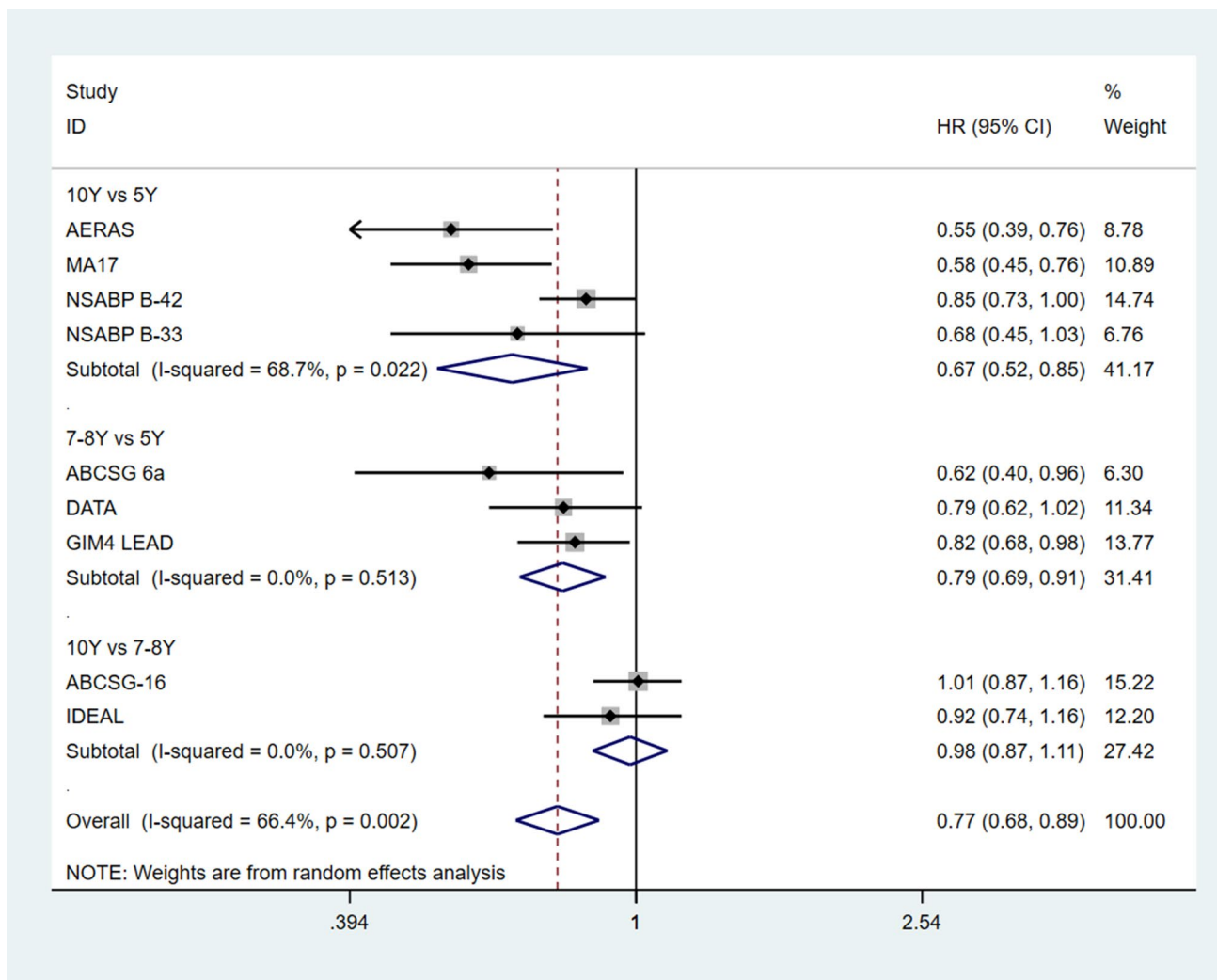
subgroup of patients, with the 95% CI of HR including one ($P \geq 0.05$) for all analysis.

Overall survival (OS)

Except for GIM4 LEAD and NSABP B-33, all other 7 RCTs enrolling a total of 18,659 postmenopausal women with HR-positive breast cancer were available for the analysis of OS. Figure 4 shows the forest plots of HR for OS generated by the fixed effects model. Our analysis revealed that the extension of adjuvant endocrine therapy was not associated with an decreased risk of death from any cause (HR = 1.01 [0.90, 1.13]; I^2 = 0.0%, fixed effects model), no matter extension

Fig. 3 Forest plot of the hazard ratio of DFS stratified by the whole duration of endocrine therapy. Pooled values were from random-effect analysis, except for the comparisons between 7–8 and 5 years and between 10 and 7–8 years, which were from fixed-effect analysis because of low heterogeneity. *Y* years, *HR* hazard ratio, *CI* confidence interval

in study AERAS, MA17 and NSABP B-42, respectively; HR for 7–8 years vs 5 years: 0.53 [0.29, 0.96] reported in study ABCSG 6a) could be reduced significantly by AI extension [10, 12, 17, 24]. Due to data limitation, whether local recurrence and contralateral breast cancer can be reduced by AI extension needs further investigation.

As to the comparison between 10 and 7–8 years, we found that the DFS of extending to 10 years was not significantly better than that of extending to 7–8 years. Study SOLE, which is not included in this meta-analysis because of its intermittent extending design, indicated that the effect of extending letrozole by 5 years continuously was not significantly better than that of extending letrozole by 5 years intermittently, which can also support our findings to some extent [21]. However, numerically the HR for 10 years vs 5 years is better than that for 7–8 years vs 5 years (0.67

vs 0.79). Due to the limited number of studies comparing 10 years vs 7–8 years of endocrine therapy, we cannot rule out the possibility that there might be a potential benefit of extending endocrine therapy from 7–8 to 10 years. Therefore, although statistical data shown that 7–8 years of endocrine therapy might be enough, we hold the point that more studies are in need to compare the effect of 7–8 years to 10 years of treatment.

A meta-analysis published in 2018 demonstrated that extended AI after initial endocrine therapy didn't significantly improve DFS [27]. Another meta-analysis published in 2020 revealed a significant improvement in DFS with extended AI after initial AI-containing therapy [18]. In our meta-analysis, there are four improvements: first, the above-mentioned two meta-analysis were designed to investigate whether extended AI can improve DFS, while

Table 2 Subgroup analysis of DFS

Subgroups	10 Y vs 5 Y			7–8 Y vs 5 Y			10 Y vs 7–8 Y		
	Study	HR (95%CI)	Pooled HR (95%CI)	Study	HR (95% CI)	Pooled HR (95% CI)	Study	HR (95% CI)	Pooled HR (95% CI)
Initial 5 years therapy									
5 Y Tam	MA17	0.58 (0.45, 0.76)	0.61 (0.49, 0.76)*	ABCSG 6a	0.40 (0.22, 0.73)	0.40 (0.22, 0.73)*	ABCSG-16	0.99 (0.82, 1.20)	1.00 (0.83, 1.20)
	NSABP B-33	0.68 (0.45, 1.03)					IDEAL	1.06 (0.50, 2.25)	
2–3 Y Tam→3–2 Y AI	AERAS	0.60 (0.16, 1.99)	0.74 (0.57, 0.97)*	ABCSG 6a	1.13 (0.56–2.25)	0.82 (0.71, 0.95)*	ABCSG-16	1.06 (0.84, 1.34)	1.02 (0.85, 1.23)
	NSABP B-42	0.75 (0.57, 0.99)		DATA	0.79 (0.62–1.02)		IDEAL	0.97 (0.73, 1.30)	
				GIM4 LEAD	0.82 (0.68, 0.98)				
5 Y AI	AERAS	0.55 (0.39, 0.78)	0.72 (0.44, 1.18)[a]				ABCSG-16	0.86 (0.52, 1.41)	0.82 (0.60, 1.13)
	NSABP B-42	0.91 (0.75, 1.10)					IDEAL	0.80 (0.53, 1.21)	
Node status									
Negative	AERAS	0.69 (0.35, 1.35)	0.74 (0.52, 1.06)[a]	ABCSG 6a	0.61 (0.31–1.18)	0.82 (0.56, 1.20)	ABCSG-16	1.03 (0.85, 1.23)	1.07 (0.90, 1.27)
	MA17	0.45 (0.27, 0.73)		DATA	0.94 (0.59, 1.50)		IDEAL	1.41 (0.86, 2.30)	
	NSABP B-42	0.86 (0.69, 1.07)							
	NSABP B-33	1.13 (0.57, 2.24)							
Positive	AERAS	0.51 (0.34, 0.76)	0.63 (0.48, 0.83)[a,*]	ABCSG 6a	0.61 (0.34–1.10)	0.72 (0.56, 0.93)*	ABCSG-16	0.99 (0.79, 1.23)	0.91 (0.77, 1.07)
	MA17	0.61 (0.45, 0.84)		DATA	0.75 (0.56, 1.00)		IDEAL	0.82 (0.64, 1.06)	
	NSABP B-42	0.85 (0.68, 1.06)							
	NSABP B-33	0.50 (0.30, 0.86)							
Hormone receptors status									
ER+/PR+	MA17	0.49 (0.36, 0.67)	0.54 (0.42, 0.71)*	ABCSG 6a	0.32 (0.18–0.58)	0.61 (0.47, 0.78)*	ABCSG-16	1.06 (0.90, 1.25)	1.06 (0.90, 1.25)
	NSABP B-33	0.70 (0.43, 1.14)		DATA	0.70 (0.53, 0.92)				
ER+/PR− or ER−/PR+	MA17	1.04 (0.58, 1.87)	0.86 (0.52, 1.41)	ABCSG 6a	2.93 (1.18, 7.30)	1.71 (0.71, 4.12)[a]	ABCSG-16	0.87 (0.65, 1.15)	0.87 (0.65, 1.15)
	NSABP B-33	0.52 (0.20, 1.32)		DATA	1.18 (0.71, 1.96)				
Tumor size									
0–2 cm (T1)	AERAS	0.60 (0.35, 1.04)	0.69 (0.47, 1.01)	DATA	0.91 (0.60, 1.38)	0.91 (0.60, 1.38)	ABCSG-16	1.04 (0.88, 1.24)	1.03 (0.88, 1.20)
	NSABP B-33	0.79 (0.46, 1.36)					IDEAL	0.95 (0.65, 1.39)	
≥ 2 cm (T2, T3, T4)	AERAS	0.52 (0.32, 0.81)	0.51 (0.35, 0.75)*	DATA	0.72 (0.51, 0.98)	0.72 (0.51, 0.98)*	ABCSG-16	0.92 (0.72, 1.18)	0.93 (0.77, 1.13)
	NSABP B-33	0.49 (0.24, 0.98)					IDEAL	0.94 (0.69, 1.27)	

Y years, *HR* hazard ratio, *CI* confidence interval, *Tam* tamoxifen, *AI* aromatase inhibitor, *ER* estrogen receptor, *PR* progesterone receptor

[a]Because of heterogeneity between studies, these pooled values were from random-effect analysis, while others were from fixed-effect analysis

Table 2 (continued)

*P < 0.05
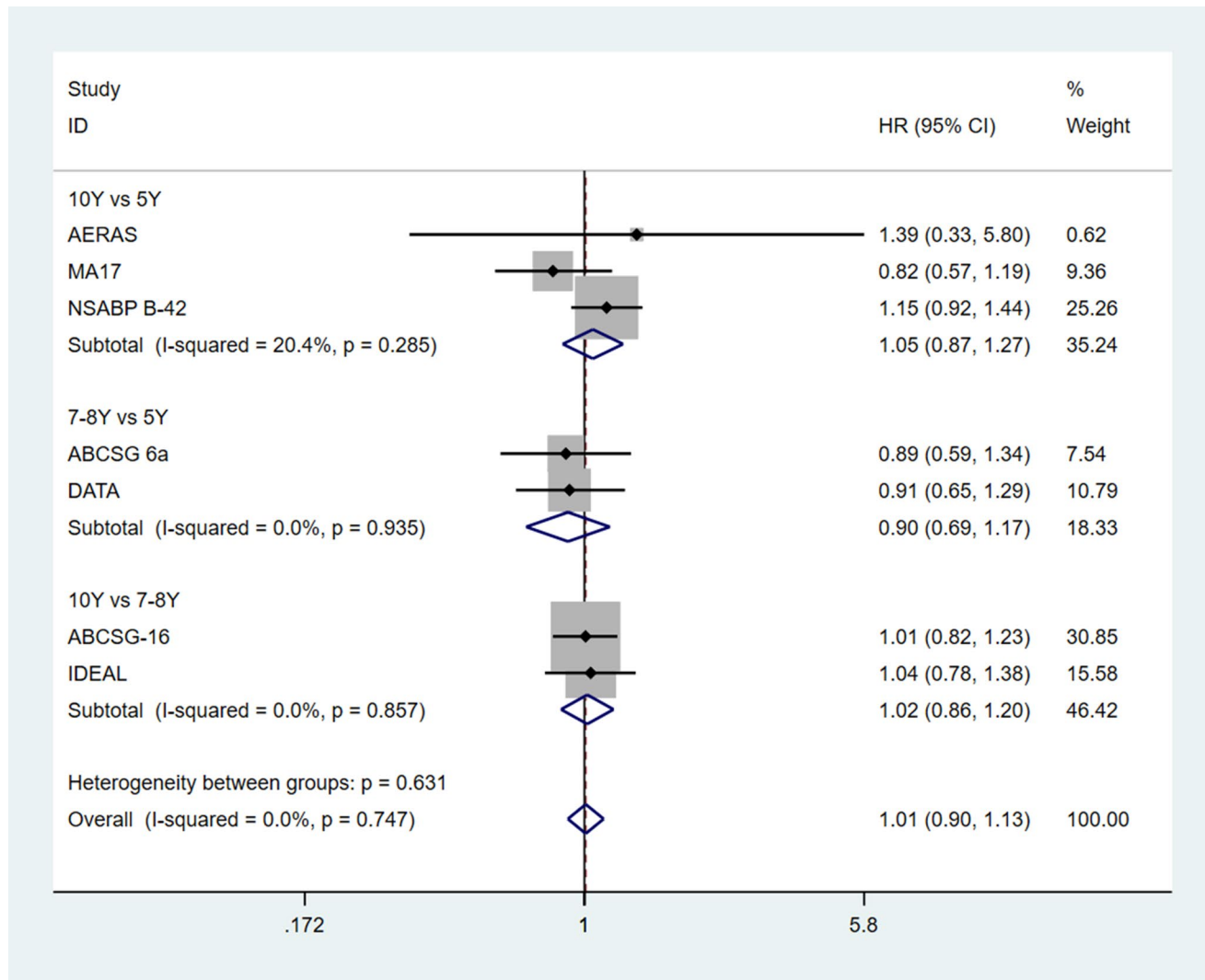
Fig. 4 Forest plot of the hazard ratio of OS stratified by the whole duration of endocrine therapy. Pooled values were from fixed-effect analysis because of low heterogeneity. *Y* years, *HR* hazard ratio, *CI* confidence interval

the duration of AI extension was not distinguished between 2–3 and 5 years, therefore, our study is the first meta-analysis exploring the optimal duration of AI extension; second, HR, a more commonly used and more suitable statistics for survival analysis, was used in our analysis; third, more stringent inclusion criteria was applied in this study, according to which study LATER was excluded because of obvious bias, and study SOLE was excluded because of the intermittent extending design; fourth, a more detailed subgroup analysis was conducted in our study, which suggesting that 5 years of endocrine therapy is enough for a certain subgroup of patients, and 7–8 years of endocrine therapy might be enough for other patients.

From the perspective of the subgroup analysis, extending endocrine therapy from 5 to 7–8 years or to 10 years couldn't reduce recurrence among patients who had been treated with AI for 5 years, with tumors that were node-negative, ER+/PR− or ER−/PR+, and < 2 cm in size. However, as to those who had been treated with only tamoxifen or sequential tamoxifen followed by an AI for a total of 5 years, with tumors that were node-positive, ER+/PR+ or ≥ 2 cm in size, extending endocrine therapy could reduce recurrence

Table 3 Pooled RR for the incidence of commonly reported adverse events

	10 Y vs. 5 Y			7–8 Y vs. 5 Y			10 Y vs. 7–8 Y		
	Study	RR (95% CI)	Pooled RR (95% CI)	Study	RR (95% CI)	Pooled RR (95% CI)	Study	RR (95% CI)	Pooled RR (95% CI)
Bone fracture	AERAS	2.44 (1.13, 5.28)	1.27 (1.05, 1.54)*	DATA	1.33 (0.97, 1.81)	1.36 (1.01, 1.84)*	ABCSG-16	1.49 (1.10, 2.00)	1.57 (1.22, 2.02)*
	MA17	1.15 (0.91, 1.47)		GIM4 LEAD	1.81 (0.61, 5.37)		IDEAL	1.79 (1.11, 2.90)	
	NSABP B-42	1.30 (0.81, 2.11)							
	NSABP B-33	1.39 (0.79, 2.45)							
Osteopenia/ osteoporosis	AERAS	1.18 (1.01, 1.37)	1.24 (1.10, 1.40)*	GIM4 LEAD	1.73 (1.22, 2.45)	1.73 (1.22, 2.45)*	IDEAL	1.70 (1.28, 2.26)	1.70 (1.28, 2.26)*
	MA17	1.35 (1.11, 1.65)							
	NSABP B-42	0.50 (0.12, 1.99)							
Bone pain (including arthralgia)	AERAS	1.63 (1.28, 2.07)	1.28 (1.11, 1.49)a,*	ABCSG 6a	1.34 (1.03, 1.73)	1.34 (1.03, 1.73)*	IDEAL	1.11 (0.88, 1.40)	1.11 (0.88, 1.40)
	MA17	1.23 (1.11, 1.36)							
	NSABP B-42	1.15 (1.00, 1.32)							
	NSABP B-33	1.99 (0.60, 6.58)							
Joint stiffness	AERAS	2.42 (1.68, 3.49)	2.40 (1.68, 3.43)*				IDEAL	0.94 (0.66, 1.35)	0.94 (0.66, 1.35)
	MA17	1.99 (0.37, 10.86)							
Myalgia	MA17	1.23 (1.07, 1.41)	1.24 (1.10, 1.39)*						
	NSABP B-42	1.26 (1.00, 1.59)							
Alopecia	MA17	1.42 (1.09, 1.85)	1.42 (1.09, 1.85)*				IDEAL	0.91 (0.64, 1.30)	0.91 (0.64, 1.30)
Depression	MA17	1.09 (0.87, 1.38)	1.12 (0.89, 1.39)				IDEAL	0.82 (0.56, 1.19)	0.82 (0.56, 1.19)
	NSABP B-42	1.39 (0.62, 3.13)							
Hypertension	MA17	1.01 (0.80, 1.28)	1.00 (0.81, 1.24)						
	NSABP B-42	0.96 (0.57, 1.61)							

Y year, *RR* risk ratio, *CI* confidence interval

aBecause of heterogeneity between studies, this pooled value was from random-effect analysis, while others were from fixed-effect analysis.

*$P < 0.05$

significantly. Patients with tumors that are node-positive, ER+/PR+ or ≥ 2 cm in size may face a higher risk of recurrence, and therefore obtain more benefit from extended therapy [26]. In recent years, many studies investigating the predicting value of biomarkers have been conducted [28–30]. In the future, tools that can accurately predict the risk of recurrence need to be developed to further facilitate the selection of patients who should receive extended endocrine therapy in clinical practice.

The results of OS in this meta-analysis indicated that extending endocrine therapy, whether to 7–8 years or to 10 years, did not bring survival benefit. That is to say, the benefit of extended endocrine therapy in reducing recurrences cannot be translated into survival benefit, which

has been supported by all studies included in this meta-analysis. A proper reason is that the follow-up period is not long enough. For early-stage breast cancer, a disease with relatively high survival rate, endocrine therapy might have a carryover effect on overall survival which increases over time [4]. It is not surprising that it is difficult to observe OS benefits during a relatively short follow-up period of time.

Our meta-analysis shows that higher risk of bone fracture, osteoporosis and bone pain may be caused by the extension of endocrine therapy, which has been reported in many previous studies [31–33]. It means that the extending of endocrine therapy is not an easy choice for patients and there should be a balance between toxicities and benefits in clinical practice. For patients who need to receive extended endocrine therapy, bisphosphonates, cholecalciferol and calcium supplementation can be administrated to protect bone health.

The main limitation of this study is the number of studies included in the analysis. A total of 9 studies were included, but after being classified into three categories, only 2–4 studies were included in each category. Extending endocrine therapy from 7–8 to 10 years didn't lead to significant improvement in DFS is an important finding that should be paid attention to by clinicians, but this finding is only supported by 2 studies. Considering the non-significant but numerically better HR for 10 years vs 5 years than that for 7–8 years vs 5 years, more studies comparing the effect of 7–8 to 10 years are in need to further confirm this finding. The second limitation is that the data of GIM4, ABCSG-16 and AERAS trials were from conference presentations instead of published papers. We included these trials because of the limited number of published studies. After the publication of more detailed data for these studies and other similar studies in the future, more published results should be included in future meta-analysis. Another limitation is that the definition of DFS are not the same for all included studies, which may cause heterogeneity. Specifically, the definition of DFS in ABCSG 6a and MA 17 does not include death, which was different from other studies. Considering the limited number of studies, we included these two studies in our analysis.

Even with the above-mentioned limitations, our data suggests that patients who have been treated with AI for 5 years, with tumors that are node-negative, ER+/PR− or ER−/PR+, and < 2 cm in size do not need to receive extended AI therapy. For those who have been treated with only tamoxifen or sequential tamoxifen followed by an AI for a total of 5 years, with tumors that are node-positive, ER+/PR+ or ≥ 2 cm in size, 2–3 years of extended AI is necessary and maybe enough. We hope that our research results can attract more attention, and stimulate more studies comparing the effect of 7–8 years versus 10 years of treatment, so that the optimum duration of endocrine treatment can be further clarified.

Compliance with ethical standards

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Affiliations

Juan Chen[1] · Xiaohui Zhang[2] · Yan Lu[1] · Ting Zhang[1] · Zhaolian Ouyang[1] · Qiang Sun[2]

[1] Institute of Medical Information/Medical Library, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2] Department of Breast Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China