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Optimal extension time after initial endocrine therapy for postmenopausal hormone receptor-positive early-stage breast cancer: a systematic review and meta-analysis

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Abstract

Background The optimal duration of extended endocrine therapy (ET) for women with hormone receptor-positive (HR-positive) early-stage postmenopausal breast cancer remains uncertain. This meta-analysis systematically evaluated the optimal time to prolong aromatase inhibitors (AIs) therapy for postmenopausal early stage breast cancer who received initial endocrine therapy.

Methods PubMed, Web of Science, Ovid, Scopus, EmBase, and Cochrane Library were searched for randomized controlled trials (RCTs) using keywords related to breast cancer, HR-positive, AIs, and tamoxifen (TAM). Disease-free survival (DFS) was used as the primary endpoint. Meta-analysis was performed using STATA 16.0 and Revman 5.4 statistical software. Hazard ratio (HR) with its corresponding 95% confidence intervals (CI) was used as an effective indicator to assess DFS, OS, and subgroups of extended ET. Relative ratio (RR) was used to assess adverse events.

Results The study included four RCTs involving 8,748 patients with HR-positive breast cancer. Pooled data showed an improvement in DFS when extending endocrine therapy from 5 to 7–8 years (HR = 0.82, 95% CI: 0.73 ~ 0.93), especially in patients with tumor size ≥ 2 cm (HR = 0.69, 95% CI: 0.49 ~ 0.98), estrogen receptor (ER) and progesterone receptor (PR) positive (HR = 0.77, 95% CI: 0.67 ~ 0.89), human epidermal growth factor receptor 2 (HER-2) positive or negative (HR = 0.85, 95% CI: 0.74 ~ 0.97; HR = 0.44, 95% CI: 0.22 ~ 0.89) and previous chemotherapy (HR = 0.80, 95% CI: 0.68 ~ 0.95). However, DFS has not improved with the extension from 7–8 to 10 years (HR = 0.97, 95% CI: 0.85 ~ 1.10). Furthermore, we found no significant difference in overall survival (OS), adverse events (AEs) analysis revealed a significant increase in the incidence of arthralgia, osteoporosis, bone fractures and asthenia after extended AIs.

Conclusions The proportion of patients with breast cancer receiving ET extended beyond 5 years has increased, while the extension of AIs treatment from 5 to 7–8 years may be an option for high-risk patients with well-tolerated tumor size ≥ 2 cm, HR-positive, and previous chemotherapy. However, a variety of adverse events may accompany ET therapy, the identification of factors that may benefit breast cancer patients requires further randomized controlled studies.

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Keywords Breast Neoplasm, Postmenopausal Period, Duration, Aromatase Inhibitors, Randomized controlled trial

Introduction

Breast cancer is the most prevalent form of cancer among females, comprising around 25% of all female malignancies and surpassing lung cancer in incidence [1, 2]. About 60%-70% of all breast cancers are hormone receptor-positive (HR-positive) [3], is treated with endocrine therapy (ET) as a key component, significantly improving patient prognosis [4, 5].

For patients with HR-positive early-stage breast cancer (histologically confirmed stage I-III and operable invasive breast cancer with no recurrence or metastasis, estrogen receptor(ER) and/or progesterone receptor (PR)-positive, accounting for 10% of the nucleus) [6], selective estrogen receptor modulator tamoxifen (Tamoxifen, TAM) adjuvant therapy has the potential to decrease the likelihood of breast cancer-related death by about one-third over 15 years [7]. Aromatase inhibitors (AIs), primarily used to inhibit aromatase after menopause and block the conversion of androgen to estrogen, are more effective in ET than TAM and can reduce the recurrence rate by about 30% [8]. The ATAC [9] trial suggested that 5-year AIs treatment could substantially elevate disease-free survival (DFS) and reduce the risk of recurrence compared with 5-year TAM, which established the standard status of AIs as an adjuvant ET for postmenopausal patients with early-stage breast cancer. Despite these improvements in the prognosis, more than 50% of patients with HR + breast cancer still face the risk of recurrence after 5 years of ET [10]. Clinical trials have shown that prolonged ET can reduce the risk of recurrence rate and mortality for HR-positive breast cancer Patients [11, 12]. However, It is unclear which patients should receive extended treatment and for how long.

In recent years, the optimal duration of ET for postmenopausal patients with early-stage breast cancer has been a hot topic of significant research [13]. Several clinical trials have evaluated the effectiveness of prolonging the duration of ET [14]. The optimal duration of extended AIs therapy is still controversial [15]. This study performed a meta-analysis of RCT to evaluate the effectiveness of prolonging AIs therapy for various years following initial adjuvant ET.

Methods

Methods of literature search

The PRISMA statement was followed for reporting, offset risk assessment, and meta-analysis [16]. The study performed a literature search in May 2022 to identify relevant RCTs in PubMed, Web of Science, Ovid, Scopus, EmBase, and Cochrane Library databases. The search strategy included a combination of free words and subject words related to the extended time of ET for HR (+) breast cancer. The keywords used were "Breast Neoplasm", "Postmenopausal Period", "Duration", "Aromatase Inhibitors", "Tamoxifen", and "Randomized controlled trial".

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Studies that were RCTs conducted in English. (2) Studies that enrolled patients who had received prior ET for 3–5 years, including TAM and/or AIs, no obvious disease recurrence. (3) Intervention: The experimental group received extended ET for 5–6 years, and the control group received the same treatment for 2–3 years. (4) Outcome indicators: Primary endpoint was DFS, secondary endpoints were OS(as defined as the period from randomization to death), adverse events. (5) Studies that provided complete trial data.

Excluded criteria: (1) Studies that were not RCTs. (2) Studies that had a significant risk of bias: publication bias, selection bias, extraction bias, time lag bias and reporting bias. (3) Studies in which the extended ET were not AIs. (4) Studies in which prior adjuvant ET were given longer than 5 years. (5) Ongoing studies whose results were not presented or published during the literature search.

Study screening

Using the databases above, we retrieve relevant articles, and duplicates were removed. Such as reviews, conference abstracts, updates, and meta-analyses, were excluded. Afterwards, the remaining articles were reviewed by two investigators who independently assessed their titles and abstracts to eliminate any articles that did not fulfill the inclusion and exclusion criteria. Finally, articles eligible for the study were included, and a third party resolved any discrepancies.

Data extraction

Data extraction included the following information: (1) Basic information: Authors' names, publication dates, and scientific categories. (2) Study subjects: Total sample size, study design, follow-up time, median age, tumor size, histological grade, lymph node status, and hormone

receptor (ER/PR, HER2) status of the study subjects in the trial and control groups. (3) Interventions: Treatment regimens in the trial and control groups. (4) Outcome indicators: Primary endpoint was DFS Secondary endpoints were OS and adverse events.

Quality assessment

Two academics separately evaluated the risk of bias and cross-checked the results. Study risk of bias was assessed using the Cochrane tool embedded in Review Manager 5.4. Each study was judged according to low risk, unknown risk, or high risk of bias, which included selection bias, implementation bias, measurement bias, follow-up bias, reporting bias, and other biases.

Statistical analysis

Our statistical analysis was conducted using STATA 16.0 and Revman 5.4. Outcome indicators: DFS, OS and adverse events. Additionally, the subgroup analysis of DFS was performed based on tumor size (<2 cm, ≥ 2 cm), lymph node status (negative, positive), hormone receptor status (ER + and PR +, ER + or PR +), HER2 status (negative, positive) and chemotherapy (yes/no). Hazard ratio (HR) with its corresponding 95% confidence intervals (CI) was used as an effective indicator to assess DFS, OS, and subgroups of extended ET [17]. Relative ratio (RR) was used to assess adverse events. Heterogeneity test analysis was performed for the included studies, and the magnitude of heterogeneity was quantified using *P*-value and I^2. A *P*-value < 0.1 or $I^2 > 50\%$ indicated obvious heterogeneity. Whenever $P \geq 0.1$ and $I^2 \leq 50\%$, the fixed-effect model was used. Finally, funnel plots were generated, and the Egger test was performed using STATA 16.0 software to assess publication bias [18].

Results

We retrieved 5,794 articles by computer searches of PubMed, Web of Science, Ovid, Scopus, EmBase, and Cochrane Library databases. After removing duplicates, reviews, conference abstracts, updates, and meta-analyses, 56 articles remained for further evaluation based on titles and abstracts. After thoroughly assessing the full texts, the inclusion and exclusion criteria were not met by 52 articles. This study ultimately included 4 large RCTs, and the article selection process is visually represented in Fig. 1 using the PRISMA flow diagram.

Four RCTs with 8,748 patients were included in this study [24, 28–30]. Table 1 presents a summary of these studies' key characteristics. We utilized the risk of bias assessment tool available in the Cochrane Evaluation

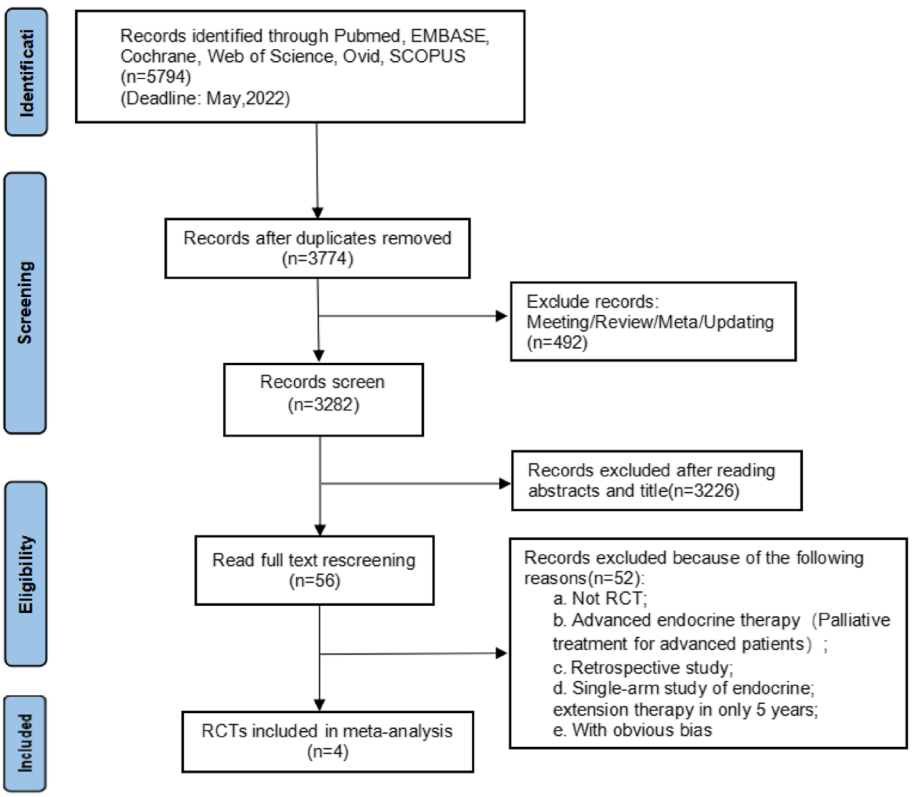

Fig. 1 Flowchart of enrolment

Table 1 Baseline patient characteristics by trial

Trial Author/ Year	Trial Design	Number of patients	Trail Patient	Previous treatment	Study Group	Control group	Median age (years)	Nodal status	Tumor stage	Tumor grade	ER status	HER2 status	median follow-up	Primary endpoint
ABCSG-16 Gnant 2021 [29]	III	3208	Postmenopausal women with HR-positive breast cancer at an early stage(I, II, or III)	TAM 5Y/ AI 5Y /TAM + AI 5y	ANA 5Y	ANA 2Y	64	66.9%N0; 30.8%N1; 1.9%N2; 0.4%N3; 0.1%unknown	72.8%T1; 25.0%T2; 1.8%T3; 0.3%Tx; 0.1%unknown	14.7%G1; 64.0%G2; 19.0%G3; 1.1%Gx; 1.3%unknown	77.7%ER-positive; 22.2%ER-negative; 0.1%unknown	No available data	118 M	DFS
IDEAL Blok 2017 [30]	III	1824	Postmenopausal women with HR-positive early breast cancer	TAM 5Y/AI 5Y/TAM + AI 5y	LET 5Y	LET 2.5Y	NG	25.9%pN0/ pN0(i +); 59.0%pN1; 14.3%pN2-3 0.8%unknown	No available data	15.7%G1; 42.5%G2; 31.1%G3; 10.7%unknown	77.4%ER-positive; 18.8%ER-negative; 3.8%unknown	68.6% HER2-negative; 30.4% HER2-positive; 1.0%unknown	6.6Y	DFS
GIM-4LEAD Lucia 2021 [28]	III	2056	Postmenopausal women with HR-positive early breast cancer	TAM 2-3Y	LET 5Y	LET 2-3Y	61 vs. 60	55.9%pN0; 40.8%pN1-2–3; 3.3%unknown	68.4%pT1; 25.0%pT2; 3.8%pT3-4; 2.8%unknown	15.4%G1; 56.1%G2; 21.1%G3; 7.4%unknown	83.7%ER-positive; 14.5%ER-negative; 1.8%unknown	81.9% HER2-negative; 6.0% HER2-positive; 12.1%unknown	11.7Y	DFS
DATA Vivianne 2023 [24]	III	1660	Postmenopausal women with HR-positive early breast cancer	TAM 2-3Y	ANA 6Y	ANA 3Y	57 vs. 57	33.1%pN0; 66.9%pN1-2–3;	45.7%pT1; 46.6%pT2; 7.5%pT3-4; < 1%Tx	18.0%G1; 51.0%G2; 28.0%G3; 3.0%unknown	76.0%ER-positive; 24.0%ER-negative	89.9% HER2-negative; 2.40% HER2-positive; 7.70%unknown	4.2Y	DFS

AI Aromatase inhibitor, *TAM* Tamoxifen, *LET* Letrozole, *ANA* Anastrozle, *ER* Oestrogen receptor, *PR* Progesterone receptor, *DFS* Disease free survival, *Y* Year, *M* Month

Manual, and all four included studies were found to have randomized groups, reported complete trial results and were rated as A for quality of the literature, suggesting mild bias, reflecting good quality of the included literature and risk of bias assessment (Fig. 2).

Primary endpoint

Disease-free survival (DFS)

The HR and 95% CI of DFS were reported in the four RCTs. Aggregated results: the analysis of DFS included in the literature suggested no heterogeneity ($P=0.24$, $I^2=29.1\%$, fixed-effect model). We observed that prolonging the duration of ET improved DFS (HR = 0.89, 95% CI: 0.82 ~ 0.97, $P=0.03$; Z = 2.22, $P<0.05$; Fig. 3A). Especially, the extension of ET from 5 to 7–8 years significantly improved DFS (HR = 0.82, 95% CI: 0.73 ~ 0.93, $P=0.002$; Z = 3.14, $P<0.05$; Fig. 3A). However, DFS has not improved with the extension from 7–8 to 10 years (HR = 0.97, 95% CI: 0.85 ~ 1.10, $P=0.607$; Z = 0.51, $P>0.05$; Fig. 3A).

Subgroups analyses of DFS

We also categorized the HR of DFS based on the following factors: tumor size (< 2 cm, ≥ 2 cm), lymph node status (negative, positive), hormone receptor status (ER + and PR +, ER + or PR +), HER2 status (negative, positive) and chemotherapy (yes, no). In the subgroup analysis of the included data, we observed an improvement in DFS when extending ET from 5 to 7–8 years in patients with tumor diameter ≥ 2 cm (HR = 0.69, 95% CI: 0.49 ~ 0.98) (Fig. 4A), PR + /ER + (HR = 0.77, 95% CI: 0.67 ~ 0.89) (Fig. 4B), HER2 ± (HR = 0.44, 95% CI: 0.22 ~ 0.89; HR = 0.85, 95% CI: 0.74 ~ 0.97) (Fig. 4C) and previous chemotherapy (HR = 0.80, 95% CI: 0.68 ~ 0.95) (Fig. 4D). The differences are summarized in Supplemental Table 1.

Secondary endpoint

Overall survival (OS)

All four RCTs reported HR and 95% CI for OS, with no heterogeneity among the studies ($P=0.30$, $I^2=17.5\%$, fixed-effects model). Our meta-analysis results revealed no significant difference in the improvement of OS (HR = 0.94, 95% CI: 0.83 ~ 1.05, $P=0.30$; Z = 2.22, $P>0.05$; Fig. 3B).

In order to evaluate the robustness of the study, we carried out sensitivity analysis, excluded some fuzzy studies and the literature of relatively poor quality from the included studies, re-conducted meta-analysis, compared whether there were significant differences before and after the merger effect. Re-analyzed the data with different statistical methods, such as using random effect model instead of fixed effect model for sensitivity analysis. It was found that no significant impact on the overall results of the meta-analysis was observed in any of the studies included. The sensitivity analysis diagram is shown in the appendix. Furthermore, the Egger bias test yielded a *P*-value of 0.47, this suggests that there is no indication of publication bias in the studies we included and that our findings are reliable.

Adverse events (AEs)

The four RCTs included in this study reported adverse events. Adverse event (AE) analysis revealed a significant increase in the incidence of arthralgia (RR = 1.14, 95% CI: 1.06 ~ 1.23), osteoporosis (RR = 1.44, 95% CI: 1.07 ~ 1.93), and bone fractures (RR = 1.36, 95% CI: 1.01 ~ 1.84) in

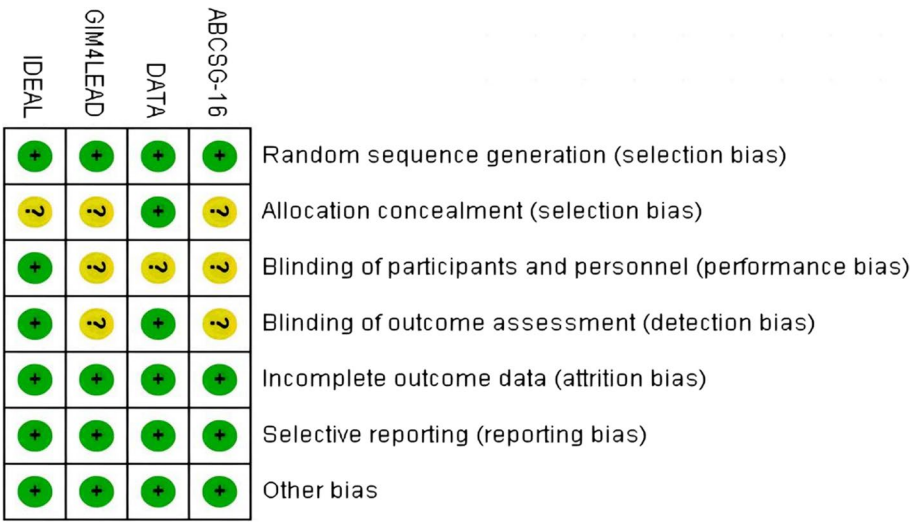

Fig. 2 Research quality evaluation chart

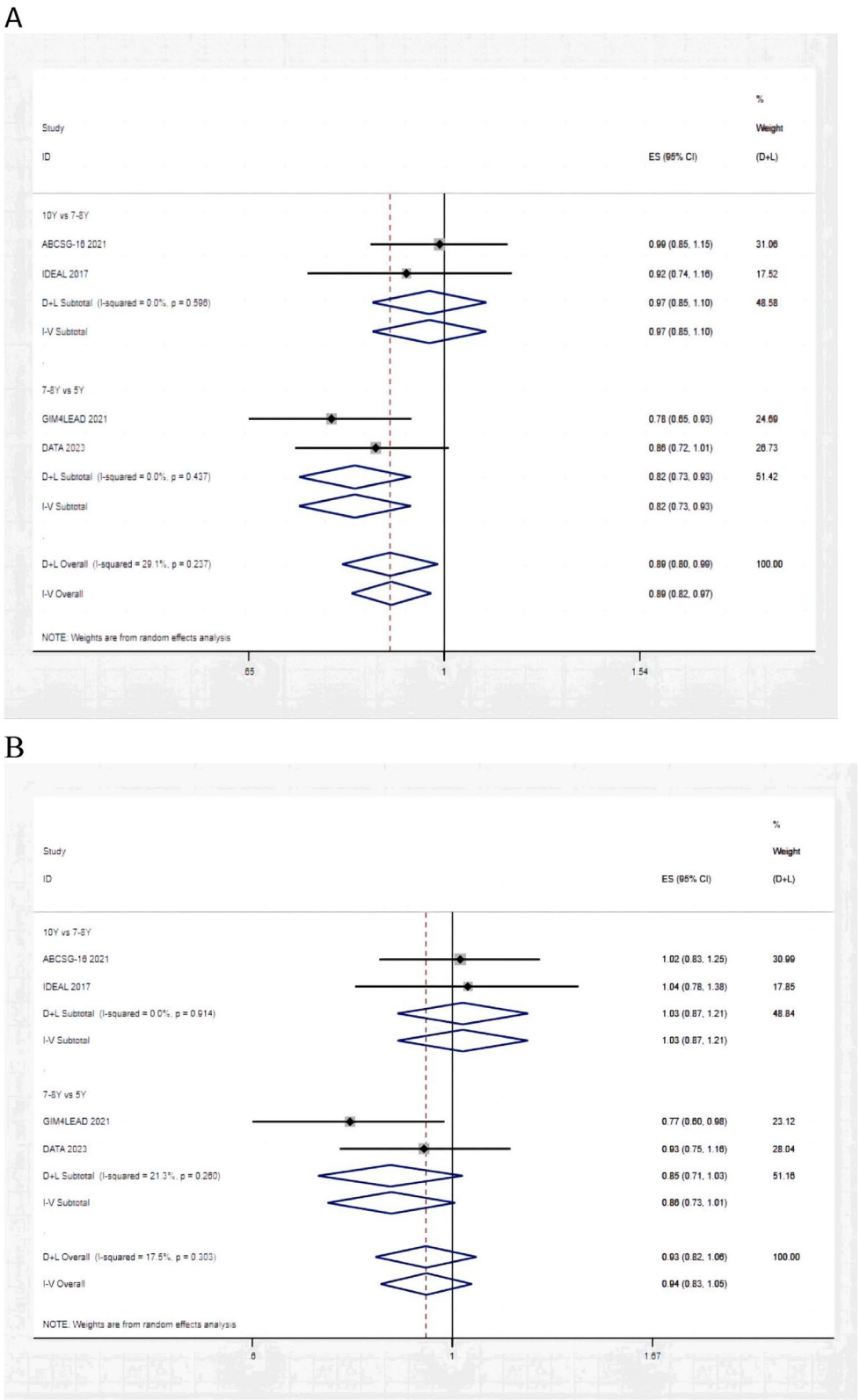

Fig. 3 Forest plot of HR in early-stage postmenopausal breast cancer patient. **A** HR for disease-free survival of all patients by the duration of endocrine therapy. **B** HR for overall survival of all patients by the duration of endocrine therapy

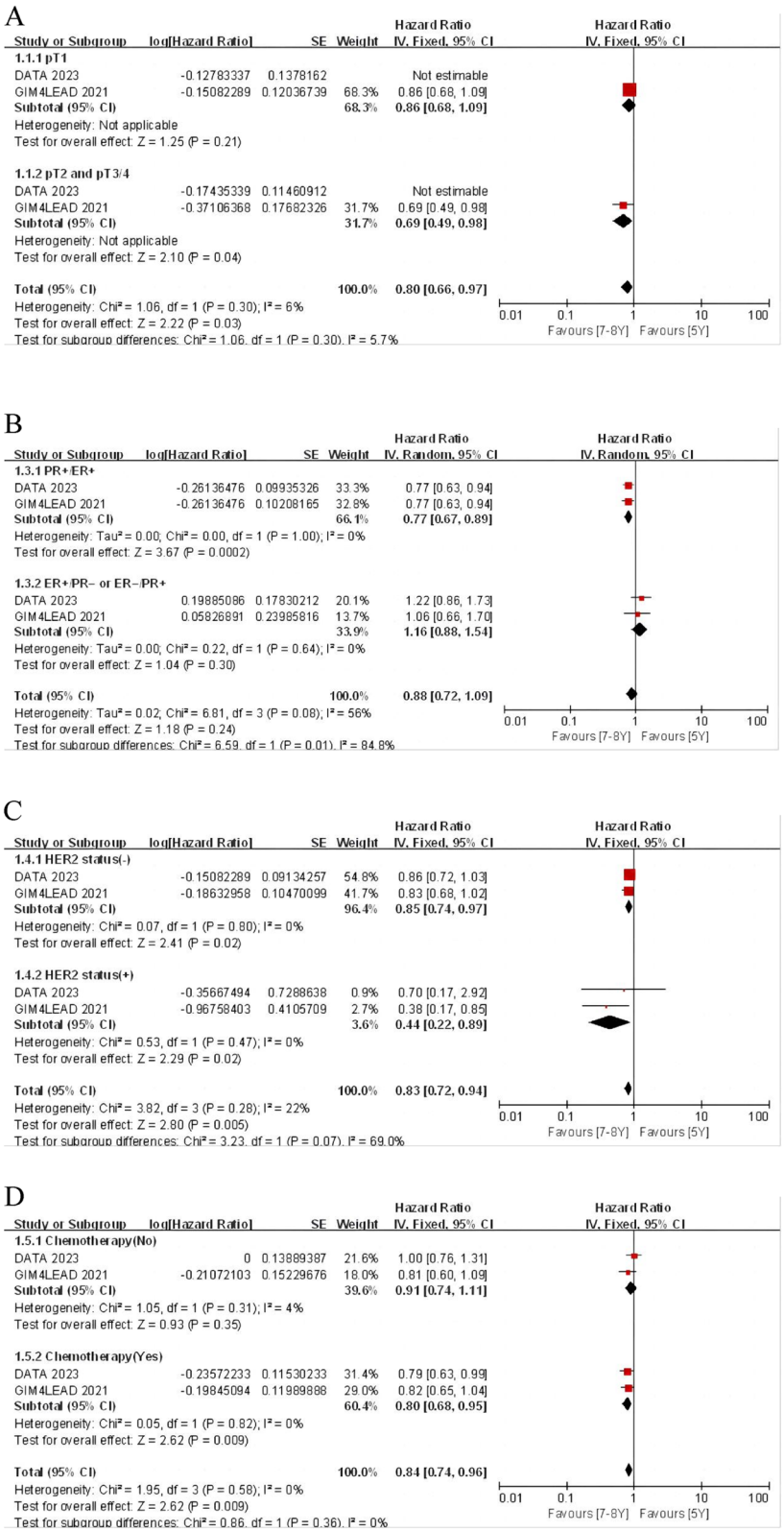

Fig. 4 Subgroup analysis of DFS. (**A**) Tumor size groups; (**B**) Hormone receptor groups; (**C**) HER2 status groups; (**D**) Chemotherapy groups

patients with ET from 5 to 7–8 years, while the incidence of osteoporosis (RR = 1.68, 95% CI: 1.27 ~ 2.22), bone fractures (RR = 1.74, 95% CI: 1.38 ~ 2.19) and asthenia (RR = 1.74, 95% CI: 1.32 ~ 2.29) is significantly increased in patients with ET from 7–8 to 10 years. The differences are summarized in Table 2.

Discussion

The optimal duration of ET for patients with HR-positive early-stage breast cancer remains controversial. Previous meta-analysis studies by Pan, Bradley [19, 20], and others have confirmed that 5 years of ET can effectively reduce the recrudescence and mortality proportion of HR(+) early-stage breast cancer. However, limited studies have investigated the extension of ET beyond 5 years.

The aTToms trial [21] showed that prolonging TAM treatment to 10 years could further reduce recrudescence and mortality proportion in female patients with HR(+) breast cancer, particularly in the second 10 years after diagnosis, with a halving of breast cancer mortality. In contrast, the NSABP-B14,NSABPB-33 trial did not find a significant survival advantage with TAM beyond 5 years [22, 23]. The DATA trial [24] included in this study revealed that the extension of AIs for 5 years after initial treatment (AI/TAM/TAM-AI) for 5 years did not significantly improve DFS and OS compared with 2.5 years. However, a study by AERAS, MA17 and Li et al. demonstrated that extending ET to 10 years after the standard 5-year ET could further improve DFS in patients with early breast cancer [25–27]. It is worth noting that drug toxicity and patient compliance can pose challenges with extended ET, and there is still ambiguity in choosing the optimal time for extending AIs treatment. This study aimed to analyze the best prolongation time after initial ET for early postmenopausal HR-positive breast cancer and to provide a reference for related clinical work.

The discoveries of this research demonstrate that extending the duration of AIs therapy from 5 to 7–8 years after the completion of initial adjuvant ET can significantly improve DFS (HR = 0.82, 95% CI: 0.73 ~ 0.93, $P = 0.002$) and decrease the disease progression by 18%, in line with the findings of the GIM4LEAD study [28]. However, ABCSG-16 and IDEAL studies demonstrated that HR(+) early breast cancer patients who completed the initial adjuvant ET continued to extend AIs therapy for 5 years without significant DFS benefit. [29, 30]. A meta-analysis evaluating OS also did not show significant benefits with extended adjuvant ET (HR = 0.94, 95% CI: 0.83 ~ 1.05, $P = 0.30$), regardless of whether it was 7–8 years or longer. This could be due to fewer studies and relatively short overall follow-up time, which may not capture long-term survival outcomes. Richman [31] showed that while extending adjuvant ET to 10 years could reduce recurrence risk in patients with HR(+) early breast cancer, no predictive biomarkers have been identified yet to determine which patients will benefit from ET. We also stratified the HR of DFS based on the tumor size(< 2 cm, ≥ 2 cm), hormone receptor status (ER + and PR +, ER + or PR +), HER2 status (negative or positive) and chemotherapy (yes or no). We found significant DFS benefits in patients with tumor diameter ≥ 2 cm, PR + / ER +, HER2 +, and formerly received chemotherapy. These findings shown that patients at high risk of recurrence after initial ET may benefit from extended AIs, while early-stage patients with smaller tumors and negative lymph nodes may achieve sufficient benefits from 5-year endocrine therapy alone. Nevertheless, it is crucial to ponder that the number of studies and follow-up duration may have contributed to these findings.

The clinical efficacy and side effects of drugs are crucial considerations while extending ET, as severe adverse reactions may affect its persistence [32, 33]. Although

Table 2 Summary of the meta-analysis of the incidence of adverse events

Adverse events	Study	7-8Y vs.5Y		Study	10Y vs.7-8Y	
		RR (95% CI)	Pooled RR (95% CI)		RR (95% CI)	Pooled RR (95% CI)
Arthralgia	GIM4LEAD DATA	1.10(1.01,1.20) 1.20(1.05,1.37)	1.14(1.06,1.23)	ABCSG-16 IDEAL	2.54(1.66,3.89) 1.11(0.88,1.40)	1.65(0.73,3.73)
Osteoporosis	GIM4LEAD DATA	1.27(1.04,1.56) 1.73(1.22,2.46)	1.44(1.07,1.93)	ABCSG-16 IDEAL	1.33(0.30,5.93) 1.70(1.28,2.26)	1.68(1.27,2.22)
Bone fractures	GIM4LEAD DATA	1.33(0.97,1.81) 1.81(0.61,5.38)	1.36(1.01,1.84)	ABCSG-16 IDEAL	1.73(1.33,2.25) 1.79(1.11,2.89)	1.74(1.38,2.19)
Asthenia	GIM4LEAD DATA	1.03(0.82,1.31) 6.04(0.73,50.05)	1.81(0.36,9.11)	ABCSG-16	1.74(1.32,2.29)	1.74(1.32,2.29)
Cardiovascular event	GIM4LEAD	1.32(0.93,1.87)	1.32(0.93,1.87)	ABCSG-16 IDEAL	2.00(0.18,22.04) 1.29(0.95,1.74)	1.30(0.96,1.75)
Mental disorder	GIM4LEAD	1.93(1.04,3.58)	1.93(1.04,3.58)	ABCSG-16 IDEAL	0.88(0.44,1.76) 0.82(0.56,1.19)	0.83(0.60,1.16)

prolonging ET can reduce the risk of recurrence in such breast cancer patients, it can also increase the occurrence of other adverse events, such as fractures and cardiovascular disease [34]. The IDEAL study found that 15.7% of patients terminated Letrozole treatment for 2.5 years due to severe adverse drug reactions [30], while the MA17R [35] study showed that bone-related toxicity was more common when ET was extended to 10 years, which is consistent with our findings. Prolonged AIs treatment increases the risk of related diseases such as joint pain, osteoporosis, fracture, and fatigue [36, 37]. However, over time, poor patient compliance may limit the benefits of prolonged ET for all patients [38]. To mitigate the adverse effects on bone mineral density associated with AIs treatment, bone modifiers such as zoledronic acid and deschumab may be considered in patients undergoing extended ET [39, 40].

There are a number of limitations that must be taken into account in this study. Initially, the main limitation of this study is that the number of included studies is small, resulting in a limited overall sample size, and studies with positive results are more likely to be published, which may cause false positives or false negatives. Secondly, the definition of DFS in the included RCTs ABCSG-16 and GIM4LEAD is not clear enough, and the outcome indicators included do not report HR. There may be heterogeneity, which may lead to difficulties in data merger analysis and affect the interpretation of the results. Thirdly, there are differences in the initial ET time in the included studies, and the results of meta-analysis may be difficult to apply directly to such patients. However, considering the limited number of studies, we continue to include these studies.

To summarize, the percentage of breast cancer patients opting for extended adjuvant ET beyond 5 years has risen significantly, irrespective of whether they meet the treatment extension criteria of the current clinical guidelines [41]. For high-risk patients with good tolerance, tumor diameter ≥ 2 cm, positive tumor lymph nodes, and positive hormone receptors, extended treatment with AIs up to 7–8 years may be an option, but various adverse events may also accompany it. Further RCTs are necessary to assess the advantages and drawbacks of prolonged adjuvant ET for individuals with breast cancer.

Abbreviations

ET	Endocrine therapy
HR-positive	Hormone receptor-positive
AIs	Aromatase inhibitors
RCTs	Randomized controlled trials
TAM	Tamoxifen
DFS	Disease-free survival
HR	Hazard ratio
CI	Confidence intervals
RR	Relative ratio
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
OS	Overall survival
AEs	Adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-025-03610-9.

Supplementary Material 1.

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Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. Patient consent for publication Not applicable.

Authors' contributions
ZY contributed to selecting research directions and completing the manuscript, LLX conducted data statistics, ZKC conducted an electronic database search. GGHZ evaluated the evidence level, WXW established the inclusion and exclusion criteria, MZJ checked and edited manuscripts. The author(s) read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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