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Adjuvant ovarian suppression for premenopausal hormone receptor-positive breast cancer

A network meta-analysis

Mengjie Jiang, MD[a,*], Wuzhen Chen, MD[b,c], Yujie Hu, MD[a], Chao Chen, MD[a], Huafeng Li, MD[a]

Abstract

Background: Ovarian function suppressor (OFS) plus either tamoxifen (TAM) or aromatase inhibitor (AI) could improve the survival outcome for premenopausal hormone receptor-positive (HR+) breast cancer. However, the optimal OFS-based regimen and medication duration remain uncertain. This article aims to systematically evaluate the OFS-based adjuvant endocrine therapy for premenopausal breast cancer.

Methods: We searched several public databases from January 1980 to November 2020. A random model was adopted in this meta-analysis. We used the hazard ratio (HR) with a 95% confidence interval (CI) for the statistical analysis of efficacy. The primary outcome measures included overall survival and disease-free survival.

Results: A total of 32 articles with 37,224 cases were included in this network meta-analysis. OFS+TAM improved 5-year disease-free survival (HR –0.09, 95% CI –0.16 to –0.01) and 5-year overall survival (HR –0.18, 95% CI –0.33 to –0.03) compared with TAM monotherapy. For OFS+AI, although the 5-year disease-free survival was improved (HR –0.18, 95% CI –0.29 to –0.08), the 5-year overall survival was not improved (HR –0.13, 95% CI –0.43 to 0.18). In subgroup analysis, both OFS+AI and OFS+TAM showed a protective effect in stage I–III patients compared with stage I–II patients. For the course of therapy, OFS+TAM for 2-years could achieve clinical benefit and the best course of therapy of OFS+AI still waits for further study.

Conclusions: OFS+TAM might be a better option than OFS+AI for premenopausal intensive adjuvant endocrine therapy. Stage III patients are more suitable for the OFS-based therapy. For the medication duration, the 2-years course of OFS+TAM could be effective. This analysis provides helpful information for selecting therapeutic regimen in intensive adjuvant endocrine therapy and identifying the target population.

Abbreviations: AI = aromatase inhibitor, ANA = anastrozole, CI = confidence interval, DFS = disease-free survival, EXM = exemestane, GnRHα = gonadotropin-releasing hormone agonist, HR = hazard ratio, HR+ = hormone receptor-positive, OFS = ovarian function suppression, OS = overall survival, RCT = randomized controlled trial, RR = Relative risk, TAM = tamoxifen.

Keywords: adjuvant endocrine therapy, GnRHα ovarian function suppression, network meta-analysis, premenopausal breast cancer

1. Introduction

In women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death.[1,2] The luminal (hormone receptor-positive [HR+]) subtype is the most common subtype in premenopausal breast cancer.[3] Therefore, improving the survival of premenopausal HR+ breast cancer patients has significant clinical value. The 5 or 10-year tamoxifen (TAM) has been the standard adjuvant endocrine therapy for premenopausal HR+ breast cancer. However, TAM monotherapy is insufficient for those at high risk of premenopausal breast cancer (age <35 years, with lymph node metastasis, stage III or higher, etc).[4,5] More intensive endocrine therapy is needed for high-risk patients.

Ovarian suppression is an intensive option for endocrine therapy, which could be divided into irreversible (surgical oophorectomy or radiation ovarian ablation) and reversible (gonadotropin-releasing hormone agonist [GnRHα]) methods. Irreversible ovarian suppression is rarely used in current clinical practice. GnRHα, as a reversible ovarian function suppressor (OFS),[6] is the mainstream method.[7] GnRHα, such as goserelin, triptorelin, or leuprorelin, is an analog of luteinizing hormone-releasing hormone, which can competitively bind to the pituitary GnRH receptor and produces negative feedback to suppress follicle-stimulating hormone and luteinizing hormone levels.[6] With the publication of the SOFT-TEXT trial, OFS+aromatase

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inhibitor (AI) or TAM has attracted lots of attention as an intensive adjuvant endocrine therapy option for premenopausal breast cancer.[8–10]

The SOFT-TEXT trial included 4690 premenopausal HR+ breast cancer patients.[4,10,11] Most stage II–III patients and part of stage I patients with a high recurrence risk requiring adjuvant chemotherapy fall into the high-risk category, accounting for 57% to 66% of the SOFT-TEXT study population.[11] Both triptorelin+TAM and triptorelin+exemestane (EXM) achieved higher rates of disease-free survival (DFS) and overall survival (OS) than TAM monotherapy in high-risk patients. Although the OFS+EXM group had a higher DFS rate than the OFS+TAM group, no significant differences were found between OFS+EXM and OFS+TAM in terms of OS. The ABCSG-12 trial was also a phase III trial that recruited 1803 premenopausal HR+ breast cancer patients randomly into 2×2 groups receiving OFS (goserelin) plus either TAM or anastrozole (ANA), with or without zoledronic acid.[12] 30% of enrolled patients had metastatic lymph nodes. With a median follow-up of 7.9 years, no statistical significance was attained in DFS between goserelin +TAM and goserelin+ANA, while the goserelin+ANA group had a higher mortality rate.[13] In overweight patients, the risk of recurrence was increased by 50%. Patients prescribed goserelin +ANA had a 3-fold increased risk of death compared with patients prescribed goserelin+TAM.[14] It is still questionable whether OFS+AI is better than OFS+TAM.[15]

For the medication duration of OFS-based endocrine therapy, the ASTRRA trial included 1483 premenopausal breast cancer patients (age $\leq$45 years) and showed that OFS+TAM had better DFS and OS than TAM monotherapy.[16] The duration of OFS use in the ASTRRA study was 2 years, while in the SOFT-TEXT study it was 5 years. Positive results were obtained in both studies; therefore, the optimal duration of OFS treatment needs to be further evaluated.

According to the existing clinical evidence, the optimal OFS-based regimen and medication duration are uncertain. In this study, we collected related clinical trials and used the network meta-analysis method to systematic review the different OFS-based adjuvant endocrine therapy to figure out the optimal regimen and medication duration for premenopausal HR+ breast cancer. We wrote the report based on the PRISMA checklist of items for reporting systematic reviews and meta-analyses. We hope this study could contribute to selecting the optimal treatment regimen for intensive adjuvant endocrine therapy and identifying the target premenopausal population most likely to benefit from OFS-based therapy.

2. Methods

2.1. Search strategy and selection criteria

We searched PubMed, EBSCO, Embase, Scopus, the Cochrane Library, and relevant websites (www.clinicaltrials.gov, www.clinicaltrialresults.org, etc) for clinical trials from January 1980 to November 2020. Reference lists, conference abstracts, relevant reviews, and book chapters were also searched and checked manually. Search terms consisted of goserelin, triptorelin, gonadotropin-releasing hormone agonist (GnRHα), luteinizing hormone-releasing hormone (LHRH) analogues, ovarian suppression, ovarian function, OFS, premenopausal, breast cancer, chemotherapy, and endocrine therapy. Two investigators independently assessed the reports for eligibility. The specific inclusion criteria were as follows: randomized or quasi-randomized controlled trials (RCTs or q-RCTs), whether hidden or blinded; female patients with a pathological diagnosis of breast cancer and premenopausal or laboratory tests confirming the presence of premenopausal estrogen, if they received chemotherapy in advance; patients who received an OFS therapy intervention in at least 1 arm; patients who received TAM or AI endocrine therapy when undergoing OFS therapy; and a follow-up period that exceeded 3 months. The data of our study were screened from published studies, therefore, ethical review or informed consent were not applicable.

2.2. Data collection

Two investigators independently extracted all data with disagreements resolved in consultation with the third investigator. We pre-specified the following primary survival outcomes: OS and DFS; hazard ratio (HR) with a 95% confidence interval (CI) and other specific indicators that could be converted to HR with CI by statistical methods. The exclusion criteria were as follows: patients with other severe diseases, such as autoimmune diseases or other tumors; experimental design flaws, such as a non-randomized design; animal experiments or non-therapeutic clinical research; study dropout rate >10% or incomplete data; duplicate publication; data that cannot be converted into HR and 95% CI; and statistical method errors that cannot be corrected.

We extracted key information from the studies including: basic information of the studies; experimental design and quality assessment (random methods, blind methods, follow-up treatment, intention-to-treat analysis); clinical characteristics of the patients (sex, age, pathological staging, treatment, etc); drug intervention measures (time of administration, treatment dose, and treatment period); and outcome measures and results.

Tumor stages were made according to the standard of 8th edition American Joint Committee on Cancer anatomical staging system for patients with breast cancer.

2.3. Statistical analysis

We adopted a classic multivariable random effects model for multiple treatment comparisons by the Netmeta package (Version 1.2-1) of R software (Version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) using graph theory methodology.[17–19] A network meta-analysis can produce a closed loop comparison to assess the effectiveness of a treatment and different therapy regimens by the Netmeta package under a frequentist framework.[17] Random model was adopted and HRs with CIs were estimated from the median of the posterior distribution. We estimate a 95% CI from the 2.5^{th} and 97.5^{th} percentiles of the posterior distribution. The potential publication bias was assessed by the Begg funnel plot and the Egger linear regression test.

3. Results

A total of 786 articles were included from the literature search, of which 682 articles were excluded by reviewing the titles and abstracts (including 53 repeated articles). Fifty-five articles were excluded that were non-standard clinical trials, reviews, editorials, or that lacked a full text. Seventeen articles were excluded because the article data could not be extracted or converted (Fig. 1). Finally, 32 articles with 37,224 cases were

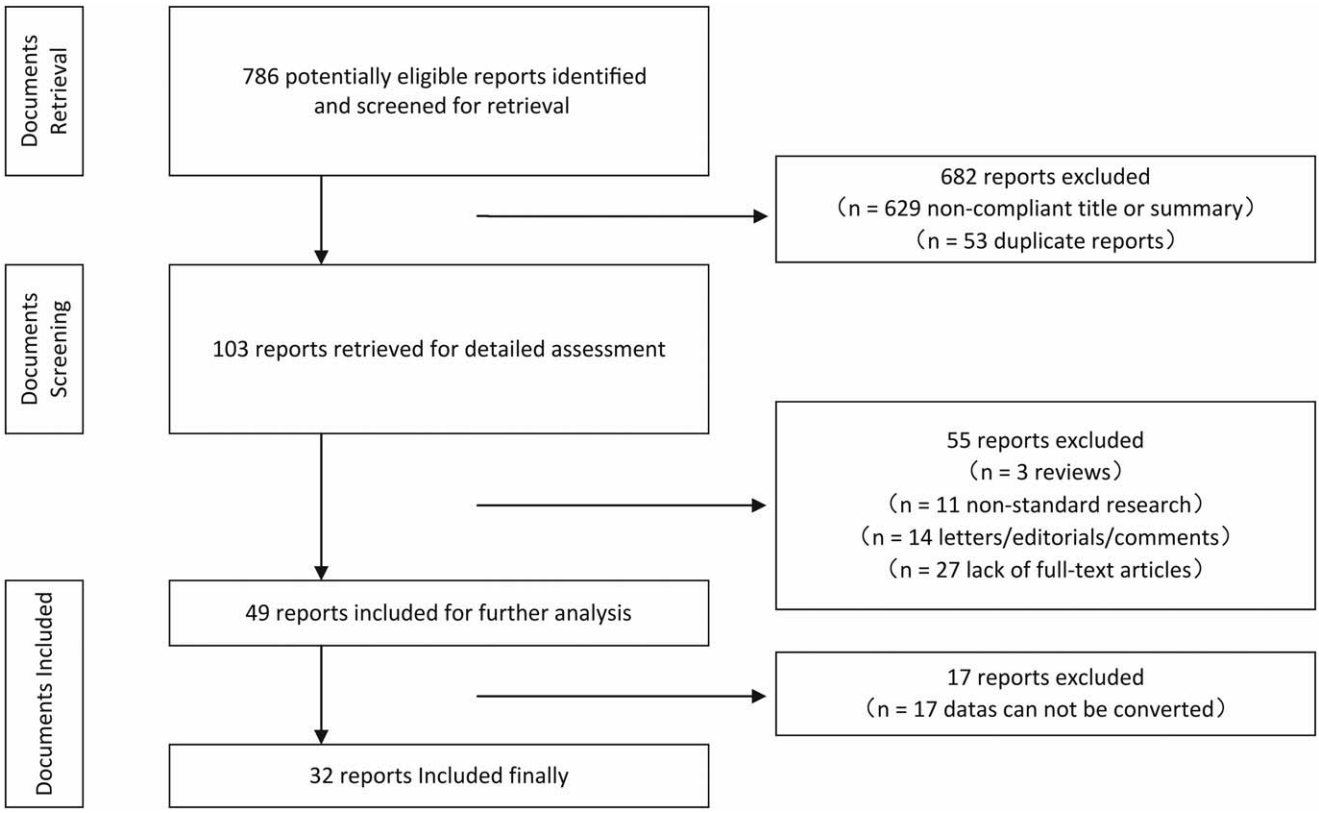

Figure 1. The PRISMA flow chart summarizing the process for the identification of the eligible studies.

Table 1

General characteristics of the trials included in the meta-analysis.

Time	Author	Stage	Treatment	OFS	Regimen (years)	Endpoint
2000	J Klijn[20]	4	OFS+TAM/OFS/TAM	Buserelin	2	DFS, OS
2001	F Boccardo[21]	3	OFS/C	Goserelin	2	DFS, OS
2001	IBCSG[58]	2	OFS+TAM+C/OFS+TAM	Goserelin	2	DFS
2002	J Soereide[23]	2	OFS/TAM	Goserelin	2	DFS, OS
2002	R Jakesz[24]	3	OFS+TAM/C	Goserelin	3	DFS, OS
2002	W Jonat[25]	2	OFS/C	Goserelin	2	DFS, OS
2003	G Pohl[59]	2	OFS+TAM/C	Goserelin	3	DFS, OS
2003	H Haes[27]	3	OFS/C	Goserelin	2	DFS, OS
2003	IBCSG[28]	2	OFS/C/OFS+C	Goserelin	2	DFS
2003	J Robertson[29]	2	OFS+TAM/OFS	Goserelin	2	DFS, OS
2003	M Kaufmann[30]	3	OFS/C	Goserelin	2	DFS, OS
2005	N Davidson[31]	2	OFS+TAM+C/OFS+C/C	Goserelin	5	DFS, OS
2005	R Arriagada[32]	3	OFS+C/C	Triptorelin	3	DFS
2005	S Placido[33]	3	OFS+TAM+C/C	Goserelin	2	OS
2006	G Minckwitz[34]	2	OFS/C	Goserelin	2	DFS
2006	H Roche[35]	2	OFS+TAM/C	Triptorelin	3	DFS, OS
2006	M Baum[36]	2	OFS+TAM/OFS/N	Goserelin	2	OS
2007	ABCTCG[37]	2	OFS+TAM/TAM	Goserelin	2	DFS, OS
2007	M Kaufmann[38]	2	OFS/C	Goserelin	2	DFS
2007	R Torrisi[39]	3	OFS+ANA/N	Triptorelin	0.5	DFS
2009	A Hackshaw[40]	2	OFS+TAM/TAM/OFS/N	Goserelin	2	DFS, OS
2010	J Wang[41]	3	OFS+TAM/TAM	Goserelin	1	DFS
2010	R Carlson[42]	4	OFS+ANA/N	Goserelin	2	DFS
2010	R Paridaens[43]	2	OFS+TAM+C/OFS+TAM	Goserelin	2	DFS
2011	A Sverrisdottir[44]	3	OFS+TAM/OFS/TAM/N	Goserelin	2	DFS
2013	H Iwata[45]	2	OFS+ANA/OFS+TAM	Goserelin	0.5	DFS
2013	R Nishimura[60]	4	OFS+ANA/OFS+TAM	Goserelin	3	DFS
2014	A Tevaarwerk[46]	2	OFS+TAM/TAM	Goserelin	5	DFS, OS
2014	D Mastro[47]	3	OFS/N	Triptorelin	2	DFS
2015	M Gnant[14]	2	OFS+ANA/OFS+TAM	Goserelin	3	DFS, OS
2018	P Francis[5]	3	OFS+EXM/OFS+TAM/TAM	Triptorelin	5	DFS, OS
2020	H Kim[16]	3	OFS+TAM/TAM	Goserelin	2	DFS, OS

ABCTCG = Adjuvant Breast Cancer Trials Collaborative Group, ANA = anastrozole, C = chemotherapy, DFS = disease-free survival, EXM = exemestane, IBCSG = International Breast Cancer Study Group, N = only postoperative follow-up, OFS = ovarian function suppressor, OS = overall survival, TAM = tamoxifen.

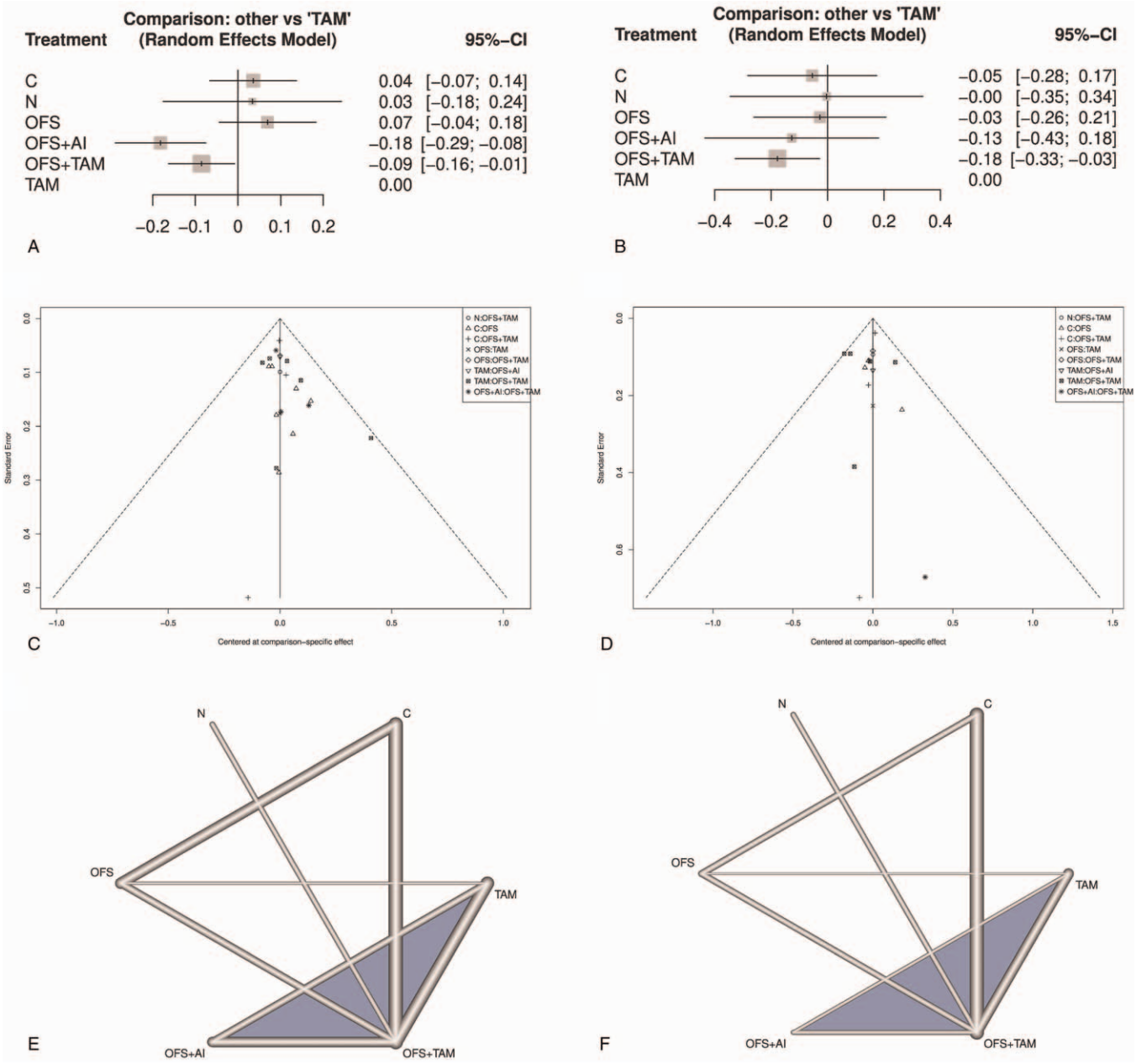

Figure 2. (A) Comparison of OFS+AI vs OFS+TAM in 5-year DFS. (B) Comparison of OFS+AI vs OFS+TAM in 5-year OS. (C) The funnel plots indicating no publication bias in DFS analysis. (D) The funnel plots indicating no publication bias in OS analysis. (E) The netgraphs for the comparison of OFS+AI vs OFS+TAM in 5-year DFS. (F) The netgraphs for the comparison of OFS+AI vs OFS+TAM in 5-year OS. AI = aromatase inhibitor, C = chemotherapy, CI = confidence interval, DFS = disease-free survival, N = only postoperative follow-up, OFS = ovarian function suppressor, OS = overall survival, TAM = tamoxifen.

included in this network meta-analysis[5,10,14,16,20–47] (Table 1 and Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A320, which illustrates the details of articles included in network meta-analysis).

3.1. OFS+TAM vs OFS+AI

Compared with TAM monotherapy, either OFS+TAM or OFS +AI could improve the 5-year DFS (OFS+TAM: HR –0.09, 95% CI –0.16 to –0.01, $P < .01$; OFS+AI: HR –0.18, 95% CI –0.29 to –0.08, $P < .01$) (Fig. 2A, C & E). For 5-year OS, patients prescribed OFS+TAM achieved survival improvement (HR –0.18, 95% CI –0.33 to –0.03, $P < .01$) (Fig. 2B, D & F). However, patients prescribed OFS+AI failed to achieve 5-year OS improvement (HR –0.13, 95% CI –0.43 to 0.18, $P = .54$) (Fig. 2B, D & F). The benefit of OFS+AI on 5-year DFS failed to translate into benefit of OS. Moreover, the CI of the OFS+AI group was large, indicating that the existing results were variable. We continued to investigate the effect of different drug combinations on the analysis outcome.

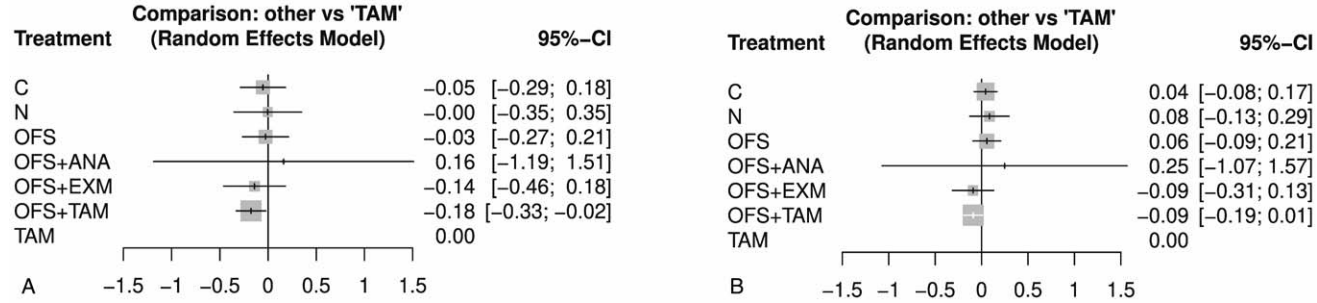

Figure 3. (A) Effects of different AIs on 5-year DFS. (B) Effects of different AIs on 5-year OS. AI = aromatase inhibitor, ANA = anastrozole, C = chemotherapy, CI = confidence interval, DFS = disease-free survival, EXM = exemestane, N = only postoperative follow-up, OFS = ovarian function suppressor, OS = overall survival, TAM = tamoxifen.

3.2. The effects of different types of AIs

The 2 major types of AIs were non-steroidal (e.g., ANA) and steroidal (e.g., EXM). Supposing that the variable results of OFS +AI were induced by different types of AIs, we further investigated different OFS+AI combinations. Neither OFS +ANA nor OFS+EXM could improve 5-year DFS (OFS+ANA: HR 0.16, 95% CI –1.19 to 1.51; OFS+EXM: HR –0.14, 95% CI –0.46 to 0.18) (Fig. 3A) or 5-year OS (OFS+ANA: HR 0.25, 95% CI –1.07 to 1.57; OFS+EXM HR –0.09, 95% CI –0.31 to 0.13) (Fig. 3B). In contrast, OFS+TAM could improve both 5-year DFS and 5-year OS (DFS: HR –0.18, 95% CI –0.33 to –0.02; OS: HR –0.09, 95% CI –0.19 to 0.01) (Fig. 3A & B). This suggests that the difference in prognosis is not due to different types of AIs.

3.3. The effects of different types of OFSs

We further investigated the effects of different OFSs on OFS+AI combinations. The 2 major types of OFSs in this analysis were goserelin and triptorelin. The analysis showed that goserelin+AI failed to show any survival benefit in 5-year DFS or 5-year OS (DFS: HR –0.10, 95% CI –0.34 to 0.15; OS: HR 0.26, 95% CI –1.08 to 1.59) (Fig. 4A & B). Compared with goserelin+AI group, the group of triptorelin+AI is superior in the 5-year DFS

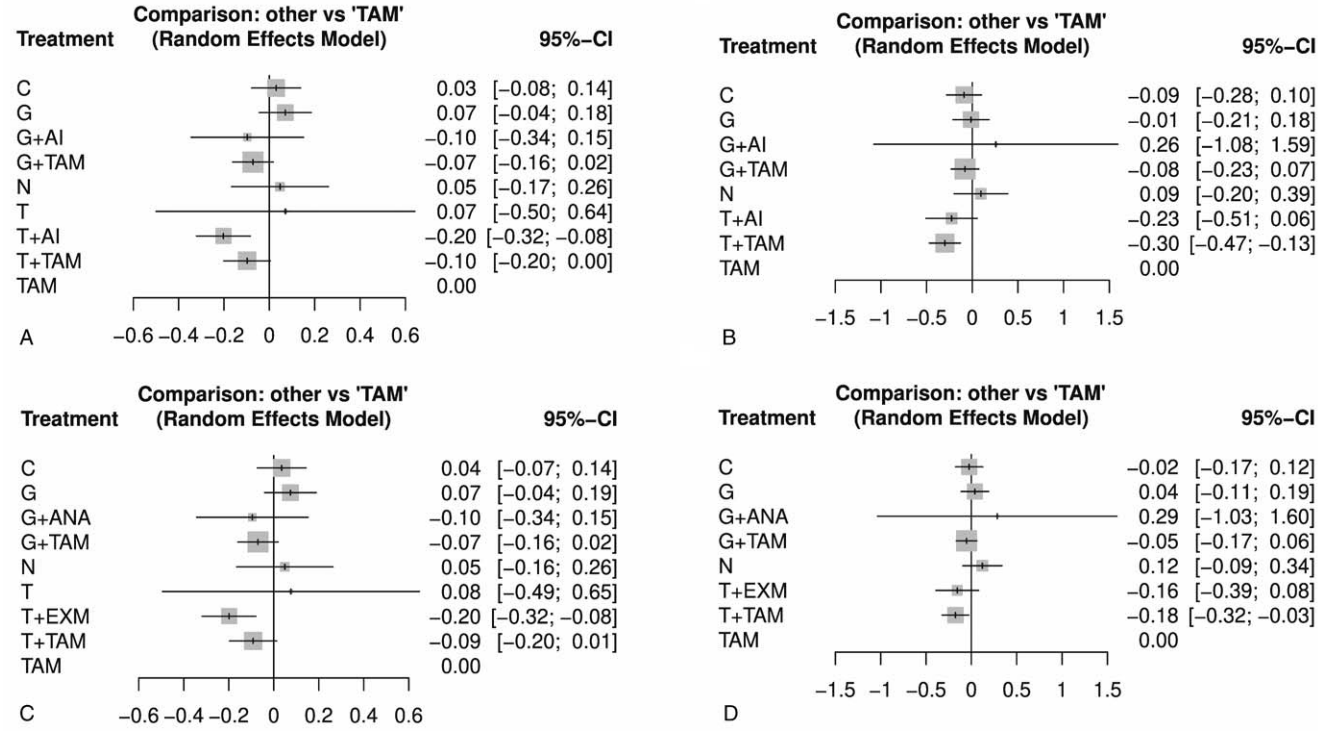

Figure 4. (A) Effects of different OFSs on 5-year DFS. (B) Effects of different OFSs on 5-year OS. (C) Effects of detailed adjuvant endocrine therapy on 5-year DFS. (D) Effects of detailed adjuvant endocrine therapy on 5-year OS. AI = aromatase inhibitor, ANA = anastrozole, C = chemotherapy, CI = confidence interval, DFS = disease-free survival, EXM = exemestane, G = goserelin, N = only postoperative follow-up, OFS = ovarian function suppressor, OS = overall survival, T = triptorelin, TAM = tamoxifen.

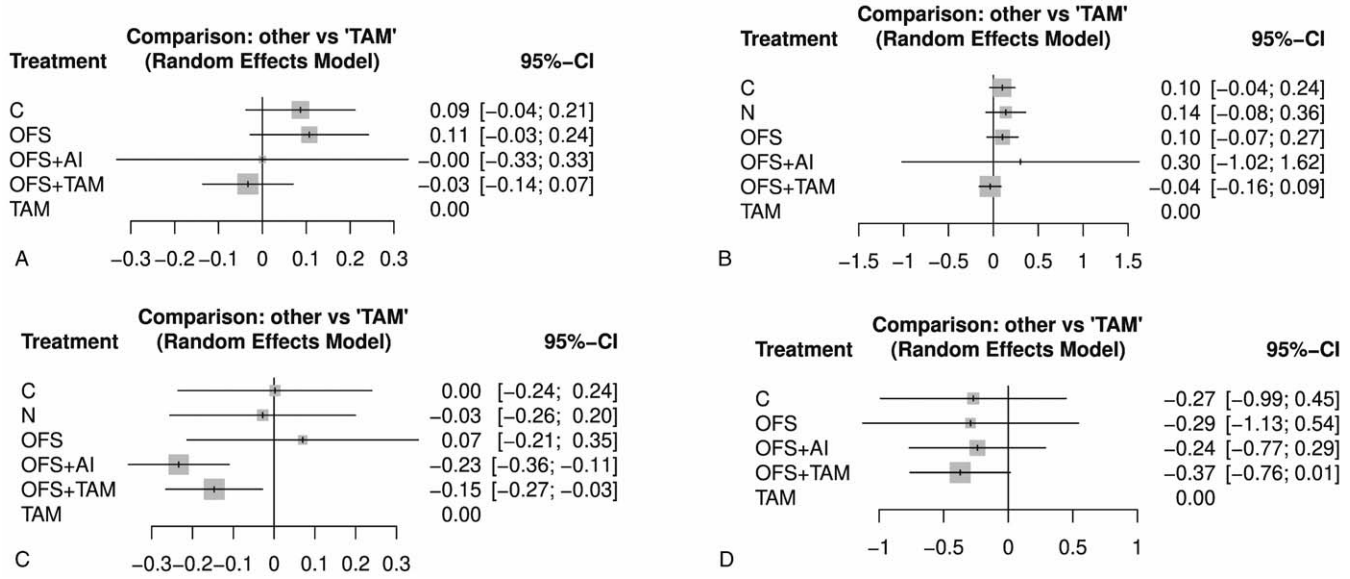

Figure 5. (A) Effects of adjuvant endocrine therapy on 5-year DFS in stage I–II. (B) Effects of adjuvant endocrine therapy on 5-year OS in stage I–II. (C) Effects of adjuvant endocrine therapy on 5-year DFS in stage I–III. (D) Effects of adjuvant endocrine therapy on 5-year OS in stage I–III. AI = aromatase inhibitor, C = chemotherapy, CI = confidence interval, DFS = disease-free survival, N = only postoperative follow-up, OFS = ovarian function suppressor, OS = overall survival, TAM = tamoxifen.

(HR –0.20, 95% CI –0.32 to –0.08) (Fig. 4A). Then we further analyzed the effects of detailed adjuvant endocrine therapy over outcome. We found that the combination of triptorelin+EXM benefit most to the DFS in various combinations of OFS+AI, although it did not translate into complete benefit for OS (DFS: HR –0.20, 95% CI –0.32 to –0.08; OS: HR –0.16, 95% CI –0.39 to 0.08) (Fig. 4C & D). Compared to goserelin+AI, triptorelin+AI could achieve 5-year DFS benefits, but the advantages in DFS could not translate into 5-year OS benefits. The SOFT-TEXT study also applied triptorelin+AI, which also reflects the same trend.

3.4. The effects of different tumor stages

Since the variation survival results of OFS+AI could not be explained by different types of AIs or OFSs, we explored the effects of different tumor stages on the survival results. Depending on the study subjects, we divided the clinical trials into 2 groups for comparison, including stage I–II patients and stage I–III patients separately (stage I–II vs stage I–III). Stage I-II patients could not benefit from OFS+AI (DFS: HR –0.00, 95% CI –0.33 to 0.33; OS: HR 0.30, 95% CI –1.02 to 1.62) or OFS+TAM (DFS: HR –0.03, 95% CI –0.14 to 0.07; OS: HR –0.04, 95% CI –0.16 to 0.09) (Fig. 5A & B). In stage I–III patients, the OFS+TAM group showed survival benefit for 5-year DFS (HR –0.15, 95% CI –0.27 to –0.03, $P < .01$) and 5-year OS (HR –0.37, 95% CI –0.76 to 0.01) (Fig. 5C & D). For OFS+AI, although the 5-year DFS was improved (HR –0.23, 95% CI –0.36 to –0.11), the 5-year OS was not improved (HR –0.24, 95% CI –0.77 to 0.29) (Fig. 5C & D). The analysis indicated that for high-risk patients (stage III), the addition of OFS to adjuvant endocrine therapy may achieve clinical benefit. Further subgroup analyses are limited by the unavailability of detailed data from included clinical trials.

3.5. The optimal regimen choice for OFS therapy

In terms of duration of medication, we found that applying OFS +AI for 5 years could improve the 5-year DFS (HR –0.20, 95% CI –0.34 to –0.06), but the benefit could not be confirmed in 5-year OS (HR –0.11, 95% CI –0.53 to 0.31) (Fig. 6). There is no significant difference between OFS+TAM treated for 2 years, 3 years, or 5 years. At present, the treatment duration of OFS+AI or OFS+TAM is still inconclusive. For OFS+AI, OFS+AI for 5-years currently has the strongest clinical evidence; for OFS+TAM, OFS +TAM for 2-years could achieve clinical benefit.

4. Discussion

According to the SOFT-TEXT trial, high-risk patients with HR+ could benefit from the use of OFS+AI than OFS+TAM. However, according to other trials, whether OFS+AI is better than OFS +TAM was still controversial. The 2016 ASCO adjuvant endocrine therapy guidelines recommended GnRHα-mediated OFS with either TAM or AI in high-risk HR+ breast cancer patients.[48] This is the first network meta-analysis to systematically evaluate the effect of different OFS-based adjuvant endocrine therapy of premenopausal HR+ breast cancer. Our analysis demonstrated that OFS+TAM could produce a greater survival benefit than OFS+AI in 5-year OS. For OFS+AI, advantages achieved in 5-year DFS were not observed in 5-year OS.

The ABCSG-12 trial showed that OFS+non-steroidal AI (ANA) had a higher risk of death, and this result may be attributed to the incomplete blockage of peripheral aromatase, especially in overweight patients.[14,49] The SOFT-TEXT trial found that OFS+steroidal AI (EXM) had a better 5-year DFS than OFS+TAM. However, there was no statistic difference between the 2 groups in terms of 5-year OS survival.[4] We think that the different pharmacological mechanisms of non-steroidal and

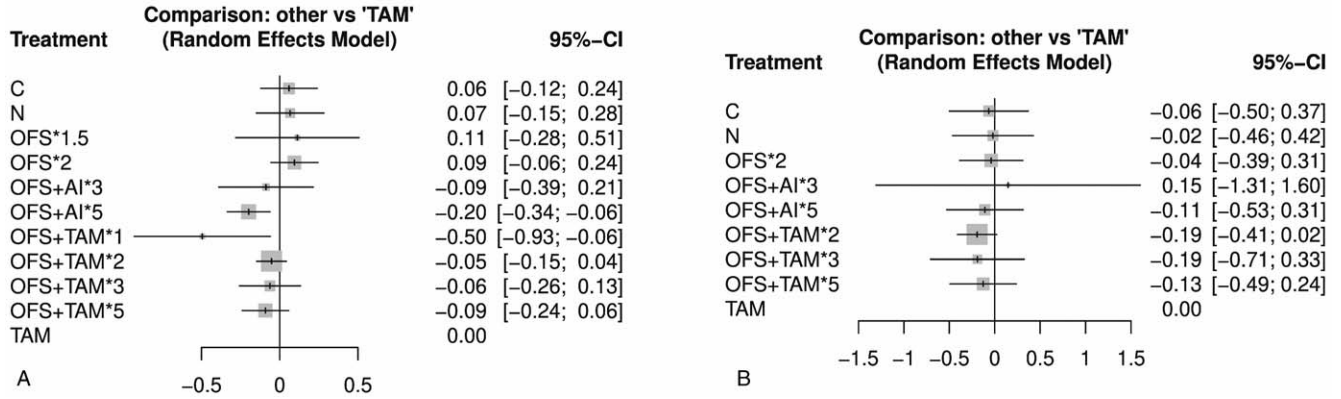

Figure 6. (A) Effects of different medication duration on 5-year DFS. (B) Effects of different medication duration on 5-year OS. AI = aromatase inhibitor, C = chemotherapy, CI = confidence interval, DFS = disease-free survival, N = only postoperative follow-up, OFS = ovarian function suppressor, OS = overall survival, TAM = tamoxifen.

steroidal AIs might partially explain the diametrically opposite results of OFS+AI in these 2 large random clinical trials.[50–52] Although SOFT-TEXT trial verified the superiority of OFS+EXM to OFS+TAM in DFS, the positive result cannot be expanded directly to all types of AIs. Long-term therapy with OFS+non-steroidal AIs could upregulate aromatase expression and restore estrogen synthesis, which induces drug resistance and survival impairment.[53,54] The SOFT-TEXT trial stated that the negative results of the ABCSG-12 trial were due to inadequate ovarian suppression by the short-term use of goserelin (only 3 years).[10] The significant improved DFS in 5-year OFS+AI group in our analysis support the longer course adjuvant endocrine treatment of OFS+AI in premenopausal breast cancer. We assessed the head-to-head comparative trials of OFS in combination with non-steroidal/steroidal AIs and planned to detect peripheral estrogen, aromatase mRNA, and aromatase activity by experiment to confirm this assumption.

Other reasons for the unsatisfied results of OFS+AI might be attributed to unclear target populations or severe adverse reactions. For the target population, the exploratory analysis of the SOFT-TEXT trial suggested that patients with high recurrence risk were more likely to benefit from OFS, especially in the young subgroup (under the age of 35) or those who pre-received chemotherapy.[4,10] Furthermore, other indicators, such as peripheral estrogen concentration or STEPP score,[11] might help physicians identify target populations.[55] For adverse reactions, the E-3193 trial showed that grade 3 or 4 toxicity, such as hot flashes, night sweats, decreased libido, muscle aches, sleep disorders, abnormal glucose tolerance, osteoporosis, and hypertension, were more common in the OFS+AI group.[14,46,49] Routine meta-analysis also suggested that the addition of OFS increases the incidence of hot flashes and osteoporosis.[56] It is unclear whether OFS+AI would produce more vital adverse reactions than OFS+TAM, which would offset potential survival benefits.

There is rare clinical trial directly comparing the different OFS-based therapy regimens. Network meta-analysis is a suitable method to solve this problem by loop comparison. In terms of medication duration, our analysis indicated that OFS+TAM treated for 2 years, 3 years, or 5 years showed no significant difference in 5-year DFS or 5-year OS. As a recently published phase III clinical trial, ASTRRA study indicated that for patients in premenopausal status after chemotherapy, the addition 2-years OFS to TAM significantly improved DFS compared to TAM monotherapy.[16] The ASTRRA study and SOFT study got the similar results of OFS+TAM is superior to TAM alone, what differed was that patients were treated with 2-years OFS in ASTRRA study, whereas in SOFT study, patients were treated with 5-years OFS. Considering the pharmaco-economics and reduction of side reactions to improve compliance of patient, we thought short-course of OFS+TAM maybe sufficient according to the existing clinical evidence.

Although this network meta-analysis is based on the datasets of various RCTs/q-RCTs for premenopausal breast cancer patients, there are still some limitations. First, although we searched the databases as completely as possible, there is still the possibility of incomplete data, especially the latest clinical trials. Second, data quality may affect our meta results. Although the included articles were carefully examined, some incomplete or low-quality data may remain in certain trials. A random-effects model and subgroup analysis were applied to address these limitations. Third, the effect of some potential confounding factors could not be analyzed due to lacking the raw data of the clinical trials. The optimization of endocrine therapy needs further validation by larger multicentric clinical trials and longer follow-ups before their application in the daily practice. Besides, research of predictive model for prognostic stratification and molecular mechanism of premenopausal HR+ breast cancer will contribute to precision adjuvant endocrine therapy.[57]

5. Conclusions

This meta-analysis indicated that OFS+TAM might be a better choice than OFS+AI for intensive adjuvant endocrine therapy in premenopausal HR+ breast cancer. The addition of OFS to adjuvant endocrine therapy is more suitable for stage III patients. For the medication duration, the 2-years course of OFS+TAM could be effective. The results could provide helpful information for optimal selection of therapeutic agents in intensive adjuvant endocrine therapy and identifying the target population. However, this study has limitations in data analysis due to the limited data from published clinical trials. More prospective clinical trials are expected to reveal the optimal OFS-based regimen and target population for intensive adjuvant endocrine therapy in premenopausal breast cancer.

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Author contributions

Mengjie Jiang designed the study, coordinated the data acquisition, planned statistical analysis, and wrote the first draft of the manuscript. Wuzhen Chen and Yujie Hu participated in data acquisition and statistical analysis. Chao Chen and Huafeng Li helped to design the study, draft and revise the manuscript. All authors read and approved the final manuscript.

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