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REVIEW

The clinical benefits of hormonal treatment for LG-ESS: a meta-analysis

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Abstract

Purpose To evaluate the clinical benefits of hormonal treatment for patients with low-grade endometrial stromal sarcoma (LG-ESS) by reviewing the published literature and performing a meta-analysis.

Methods Correlational studies related to hormonal treatment for LG-ESS patients were collected by searching the PubMed, EMBASE, and Cochrane databases up to December 2018. Eligible studies were selected based on inclusion and exclusion criteria. The main inclusion criteria included: original studies with definite diagnoses of LG-ESS that evaluated the clinical benefits of hormonal treatment, studies with at least 10 cases, and studies published in English. Reviews, case reports, letters, comments or conference abstracts, studies without sufficient data and overlapping or republished studies were excluded. The study quality was evaluated, and pooled relative risks and 95% confidence intervals were calculated using Review Manager 5.3.

Results A total of 10 retrospective studies were included. The NOS stars of the 10 studies ranged from 7 to 9 points, which was considered to be of high quality. Recurrence and death information was provided in 9 and 6 studies, respectively. The overall pooled RR for recurrence was 0.66 (95% CI 0.47–0.94), which indicated that hormonal treatment was effective at reducing the recurrence risk ($P=0.02$). The overall pooled RR for death was 0.81 (95% CI 0.59–1.12), which showed that hormonal treatment had little effect in prolonging overall survival ($P=0.20$). Stratified analysis showed that compared with the group without any adjuvant treatments, hormonal treatment alone significantly decreased the risk of recurrence ($P=0.02$), while hormonal treatment had no significant effects on overall survival ($P=0.38$). Another subgroup analysis indicated that for stage I–II patients, hormonal treatment could significantly decrease the risk of recurrence ($P=0.02$) but could not influence overall survival ($P=0.87$). However, for stage III–IV patients, hormonal treatment had little benefit both in reducing the recurrence risk and prolonging overall survival ($P=0.49/0.08$). Egger's and Begg's test showed that the publication bias for the literature was satisfactorily controlled.

Conclusion Adjuvant hormonal treatment should be considered as a feasible adjuvant therapy for reducing the recurrence risk of patients with LG-ESS while bearing little benefit on overall survival.

Keywords Adjuvant hormonal treatment · Low-grade endometrial stromal sarcoma · Recurrence · Overall survival · Meta-analysis

Introduction

Low-grade endometrial stromal sarcoma (LG-ESS) is a rare type of uterine malignancy that is classified as endometrial stromal tumors (ESS), along with benign endometrial stromal nodules, high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS) based on the current WHO classification published in 2014 [1]. Compared with HG-ESS and UUS, LG-ESS usually exhibits indolent behavior with a favorable prognosis [2]. However, regardless of the stage at diagnosis, recurrences develop in 23–59% of all LG-ESS patients [3], and an estimated

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15–25% of patients die of recurrent disease according to a systematic review [2]. In addition, a prolonged interval to recurrence after more than 10–30 years is not uncommon [4]. Because of its low incidence and indolent nature, both the surgical procedure and adjuvant treatment of LG-ESS remain controversial.

LG-ESS is sensitive to sex steroid hormones that overexpress estrogen receptors (ER) and progestin receptors (PR) [2, 5, 6]. Reich et al. [7] and Park et al. [6], respectively, reported that most LG-ESS expressed aromatase and gonadotropin-releasing hormone (GnRH) receptors. In addition, some authors indicated that ER and PR positivity was associated with significantly better overall survival [6, 8, 9]. Given that LG-ESS expresses steroid receptors and aromatases, adjuvant hormonal treatment including megestrol or medroxyprogesterone, GnRH analogs (GnRH-a), and aromatase inhibitors should be effective for reducing recurrence and prolonging survival [2, 4]. Some small series indicated that hormonal treatment could be regarded as a routine adjuvant treatment, especially for recurrent disease [5, 10–13]. Instead, some authors suggested that hormonal treatment was considered to be ineffective for disease-free survival and/or overall survival [14, 15]. There is no consensus on the role of adjuvant hormonal treatment in the treatment of LG-ESS patients. Thus, we systematically searched the related articles and performed a meta-analysis to evaluate the clinical benefits of hormonal treatment for LG-ESS patients.

Materials and methods

Adjuvant hormonal treatment was considered as any oral progestin, aromatase inhibitor, or GnRH-a [2, 16].

Search strategy

A systematic literature search in the PubMed, EMBASE and Cochrane databases was performed to collect articles related to hormonal treatment for LG-ESS patients up to December 2018. The following search terms were used: low-grade endometrial stromal sarcoma (endometrium stromal tumor* or endometrial stromal tumour* or endometrium stromal tumour* or endometrial stromal sarcoma* or endometrium stromal sarcoma* or low-grade endometrial stromal tumor* or low-grade endometrial stromal tumour* or low-grade endometrial stromal sarcoma* or endolymphatic stromal myosis or endolymphatic stromal myoses) AND hormonal treatment (adjuvant treatment* or adjuvant therap* or adjuvant hormonal therap* or adjuvant hormone therap* or adjuvant hormonal treatment* or adjuvant hormone treatment* or postoperative hormonal therap* or postoperative hormone therap* or postoperative hormonal treatment* or postoperative hormone treatment* or postoperative treatment* or postoperative therap* or observation management* or observation treatment* or observation therap* or expectant management* or expectant treatment* or expectant therap* hormone* hormon* or hormonal therap* or hormonal treatment* or endocrine therap* or endocrine treatment* or progestins or medroxyprogesterone or medroxyprogesterone acetate or megestrol acetate or aromatase inhibitors or gonadotropin-releasing hormone or GnRH-a). The reference lists of eligible articles were also searched and screened to identify other eligible studies.

Study selection

Studies were selected and included in our meta-analysis based on the following inclusion criteria: (1) original study including experimental studies (nonrandomized and randomized controlled trials [RCTs]) and observational studies (case–control and cohort studies); (2) the diagnosis of LG-ESS was confirmed by histology, pathology, or cytology; (3) the clinical benefits of hormonal treatment for LG-ESS patients were evaluated; (4) at least 10 cases were included; (5) the number of events (recurrence and/or death) was reported or could be calculated by other data; (6) the study was published in English; and (7) full text and complete data were available. The exclusion criteria were as follows: (1) reviews, case reports, letters, comments or conference abstracts; (2) studies that did not provide sufficient data; (3) published in a non-English language; and (4) overlapping or republished studies. For studies with overlapping study populations, the most recent and/or complete study was included.

Data extraction

Two reviewers independently extracted the following data parameters from the eligible studies: first author's name, publication year, study origin (country), number of included patients, pathological characteristics, surgeries, adjuvant treatments, types and approaches of hormonal treatment, follow-up period, recurrence and death. Any discrepancies between the two reviewers were resolved by discussion. A third reviewer was consulted to resolve the dispute when they failed to reach an agreement.

Assessment of study quality

The Cochrane risk of bias tool was performed to assess RCTs. The Newcastle–Ottawa scale (NOS) was used to assess the study quality of observational and nonrandomized studies. The scale includes 3 broad perspectives with a full mark of 9 stars: participant selection, comparability of study groups and assessment of outcome or exposure. Two reviewers independently assessed the study quality of the eligible

studies, and disagreements were resolved by consensus or consultation with a third reviewer.

Statistical analysis

Pooled relative ratios (RRs) with 95% confidence intervals (CIs) were calculated using Review Manager 5.3 software to assess the clinical benefits of hormonal treatment for the survival of LG-ESS patients. Heterogeneity across studies was examined using Cochran's Q statistic and the I^2 statistic. A fixed-effects model was used when a substantial level of heterogeneity ($I^2 < 50\%$) was not observed. Instead ($I^2 > 50\%$), a random-effects model was applied, and the sources of heterogeneity were explored. Subgroup analyses stratified by adjuvant treatment modalities and FIGO stage were conducted. Publication bias was assessed by Egger's and Begg's test [17]. For all tests, a two-sided P value < 0.05 was considered statistically significant.

Results

Search and selection results

A total of 1533 studies were initially retrieved based on the search strategy, including 878 in the PubMed database, 606 in Embase and 49 in the Cochrane database. The flowchart of study selection is shown in Fig. 1. Duplicate articles ($n = 295$); reviews; non-English published ($n = 72$); letters, case reports, and conference abstracts; ($n = 398$) and unrelated studies ($n = 744$) were excluded. Twenty-three studies remained for further screening of the full text. Thirteen articles were excluded for lack of required data and no response from the authors ($n = 11$) or for including overlapping study populations ($n = 2$). Ultimately, ten retrospective studies [5, 10–12, 15, 16, 18–21] that met all inclusion criteria were included for further meta-analysis.

Characteristics and study quality of included studies

The detailed characteristics of the included studies are shown in Table 1. All 10 studies were retrospective studies, and the sample sizes ranged from 10 to 2414. No RCTs or non-RCTs related to the clinical benefits of hormonal treatment for LG-ESS patients were found. The types of hormonal medication mainly included progestin (medroxyprogesterone acetate, norethisterone acetate, and megestrol acetate), aromatase inhibitor (anastrozole), and GnRH-a. The period in which the patients received hormonal treatment was unclear, and most studies did not state it definitely. The NOS stars of the 10 studies ranged from 7 to 9 points, which was considered to be of high quality.

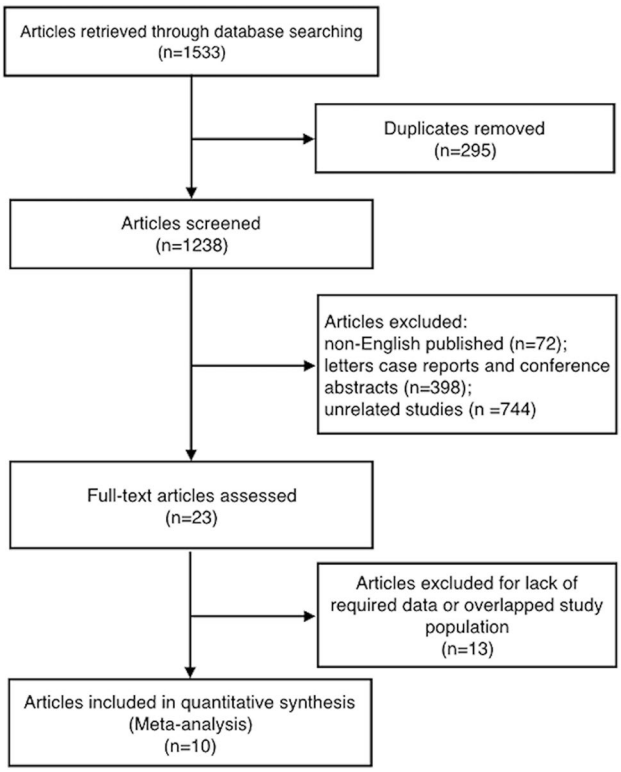

Fig. 1 Flow chart of article selection

Meta-analysis of hormonal treatment effects on the recurrence and death risk of LG-ESS patients

Recurrence and death information was provided in 9 and 6 studies, respectively. As shown in the forest plots (Fig. 2), 27% (31/115) and 36.4% (80/220) of patients suffered from recurrence in the hormonal treatment group and no hormonal treatment group, respectively. Ten percent (37/383) and 12.5% (275/2196) of patients died in the hormonal treatment group and control group, respectively. No substantial heterogeneity across these studies was detected in both the meta-analyses of recurrence and death (both $I^2 = 0\%$), and the random effects model was used. The overall pooled RRs for recurrence and death were 0.66 (95% CI 0.47–0.94) and 0.81 (95% CI 0.59–1.12), respectively. The pooled results indicated that hormonal treatment was effective at reducing the recurrence risk ($P = 0.02$) but had little effect on prolonging overall survival ($P = 0.20$).

Stratified analysis by adjuvant treatment modalities

In consideration of the effects of chemotherapy and radiotherapy on prognosis, a subgroup analysis was performed to compare the hormonal treatment alone group and the group without any adjuvant treatments, including hormonal treatment, chemotherapy and radiotherapy (observation

Table 1 The characteristics of included studies

Study	Country	Study period	Number of patients	Age (range, years)	Dosing regimen	Follow-up time (median,) (months)	Follow-up time (range) (months)	NOS star
Gadducci et al. [18]	Italy	1980.1–1994.3	26	18–68	Progestin	92	4–167	9
Huang et al. [19]	China	1965–1994	17	24–74	NA	48.1[b]	15–173	9
Chu et al. [5]	USA	1977–2002	22	19–53	Progestins	100	2–258	8
Amant et al. [10]	Belgium	1986–2005	31	18–60	Medroxyprogesterone acetate/norethisterone acetate (minimum 200 mg/day)	46.5/56[a]	7–144/2–147[a]	8
Landréat et al. [11]	France	1986–2003	10	36–68	Progestins	72	10–240	9
Beck et al. [12]	USA	1986.7–2002.9	42	27–73	NA	130[b]	NA	8
Bai et al. [20]	China	1979.7–2013.5	153	15–79	Megestrol acetate (160 mg/d)/anti-aromatase inhibitor (250 mg/d) (6 months)/GnRH-a (3 to 4 monthly injections)	74.2[b]	1–396	8
Seagle et al. [15]	USA	1998–2013	2414	43–56	NA	74.8	47.2–105.4	7
Cui et al. [21]	China	2005.1–2015.12	20	26–77	GnRH-a (3.75 mg, q28 days, 6 times)	53	9–140	8
Stewart et al. [16]	USA	1985.1–2014.12	112	22–82	NA	55	1–325	8

GnRH-a Gonadotropin-releasing hormone analog, *NA* not available

[a]With and without recurrence, respectively

[b]Mean follow-up time

group). The results showed that compared with the observation group, hormonal treatment significantly decreased the risk of recurrence in LG-ESS patients (RR = 0.63, 95% CI 0.43–0.92, $P = 0.02$), while hormonal treatment had no significant effects on overall survival (RR = 0.56, 95% CI 0.16–2.00, $P = 0.38$) (Fig. 3).

Stratified analysis by FIGO stage

Furthermore, another subgroup analysis was also performed to reduce the influence of stage on prognosis. For stage I–II patients, hormonal treatment could significantly decrease the risk of recurrence (RR = 0.57, 95% CI 0.36–0.91, $P = 0.02$), but could not influence overall survival (RR = 0.90, 95% CI 0.25–3.21, $P = 0.87$) (Fig. 4a, b). For stage III–IV patients, hormonal treatment had little benefit on both reducing the recurrence risk and prolonging overall survival (RR = 0.79, 95% CI 0.40–1.55, $P = 0.49$/RR = 0.57, 95% CI 0.24–1.32, $P = 0.08$) (Fig. 4a, b).

Publication bias

Egger's and Begg's tests were used to assess publication bias among the included studies for recurrence (9 studies) (Egger: $P = 0.912$; Begg: $P = 0.532$) and for death (6 studies) (Egger: $P = 0.700$; Begg: $P = 0.452$). The results of statistical analyses and Egger's publication bias plots showed that no publication bias existed among our included studies (Fig. 5).

Discussion

LG-ESS is the second most common malignant uterine mesenchymal tumor and occurs mainly in premenopausal and perimenopausal women [1, 22]. The primary treatment for LG-ESS patients is surgery with hysterectomy [23]. The benefits of bilateral salpingo-oophorectomy (BSO) and pelvic and para-aortic lymphadenectomy for LG-ESS remain controversial. Similarly, it has been argued whether

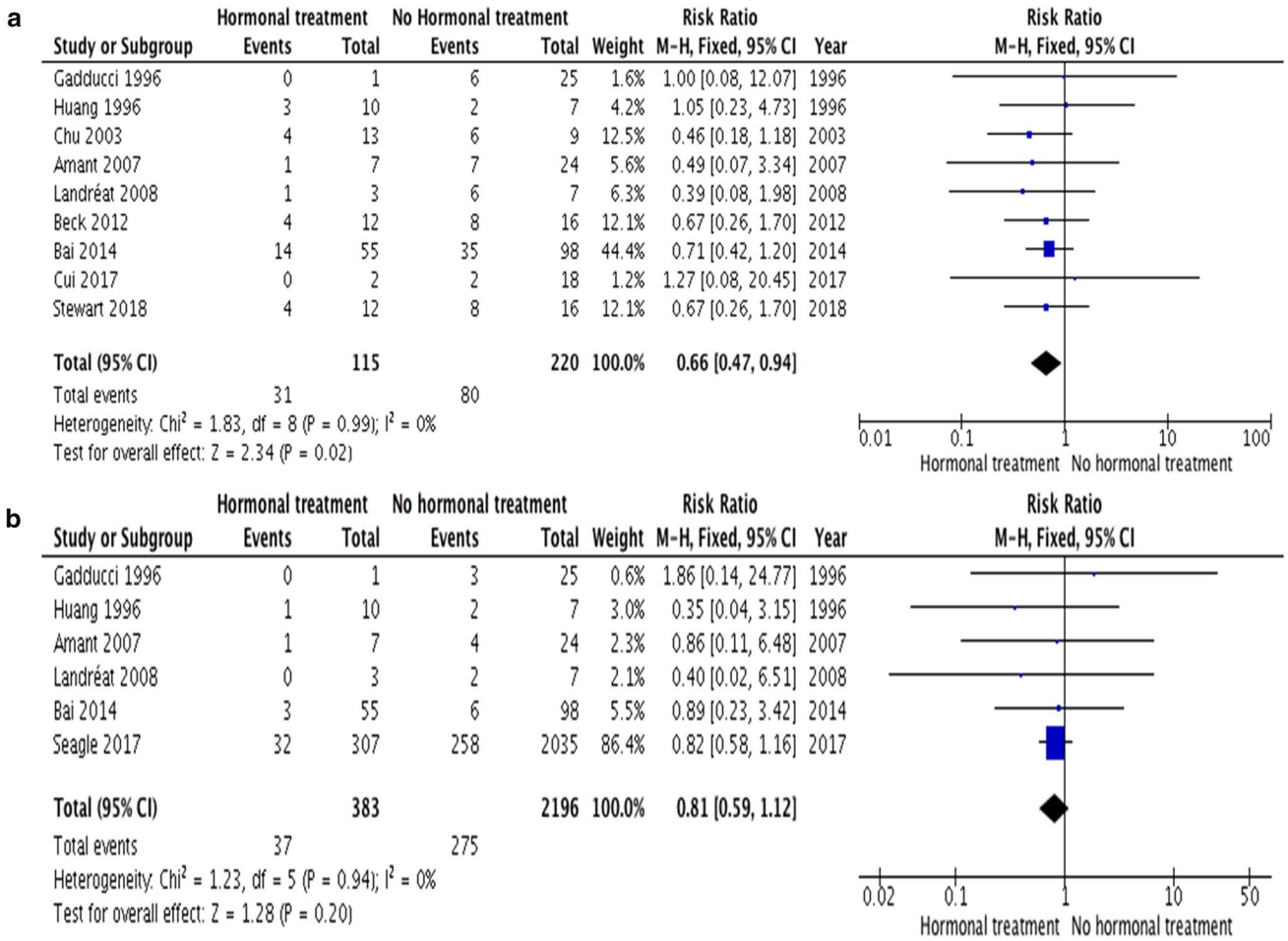

Fig. 2 Meta-analysis of hormonal treatment effects on recurrence and death risk of LG-ESS patients. Recurrence and death information was provided in 9 and 6 studies, respectively. **a** The overall pooled RR for recurrence was 0.66 (95% CI 0.47–0.94), which indicated that hormonal treatment was effective for reducing the recurrence risk (RP = 0.02). **b** The overall pooled RR for death were 0.81 (95% CI 0.59–1.12), which showed that hormonal treatment had little effect in prolonging overall survival ($P = 0.20$)

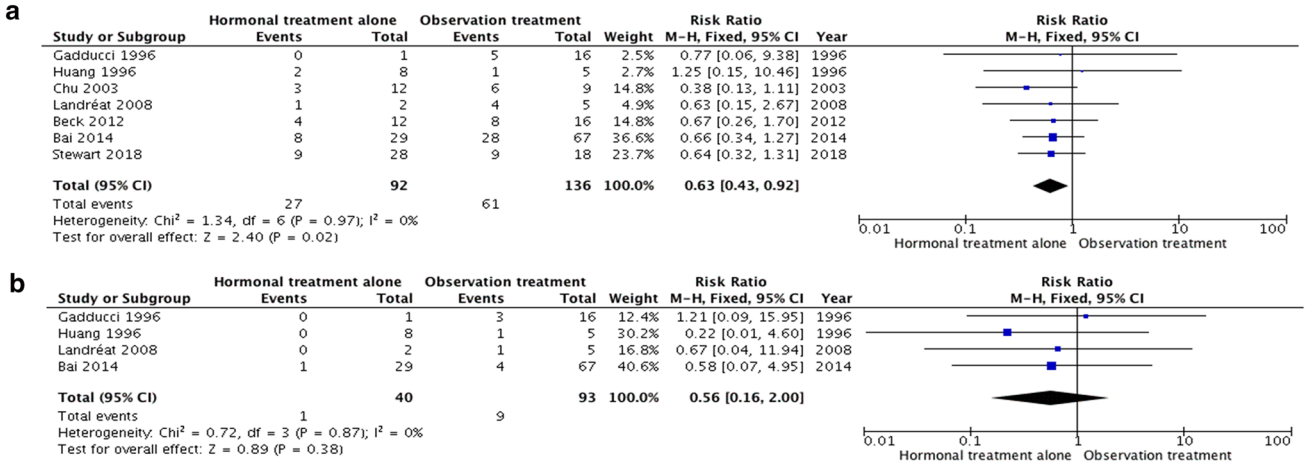

Fig. 3 Stratified analysis by adjuvant treatment modalities. **a** The subgroup analysis results showed that compared with the group without any adjuvant treatments (observation group), hormonal treatment significantly decreased the risk of recurrence (RR = 0.63, 95% CI 0.43–0.92, $P = 0.02$). **b** Hormonal treatment had no significant effects on overall survival (RR = 0.56, 95% CI 0.16–2.00, $P = 0.38$)

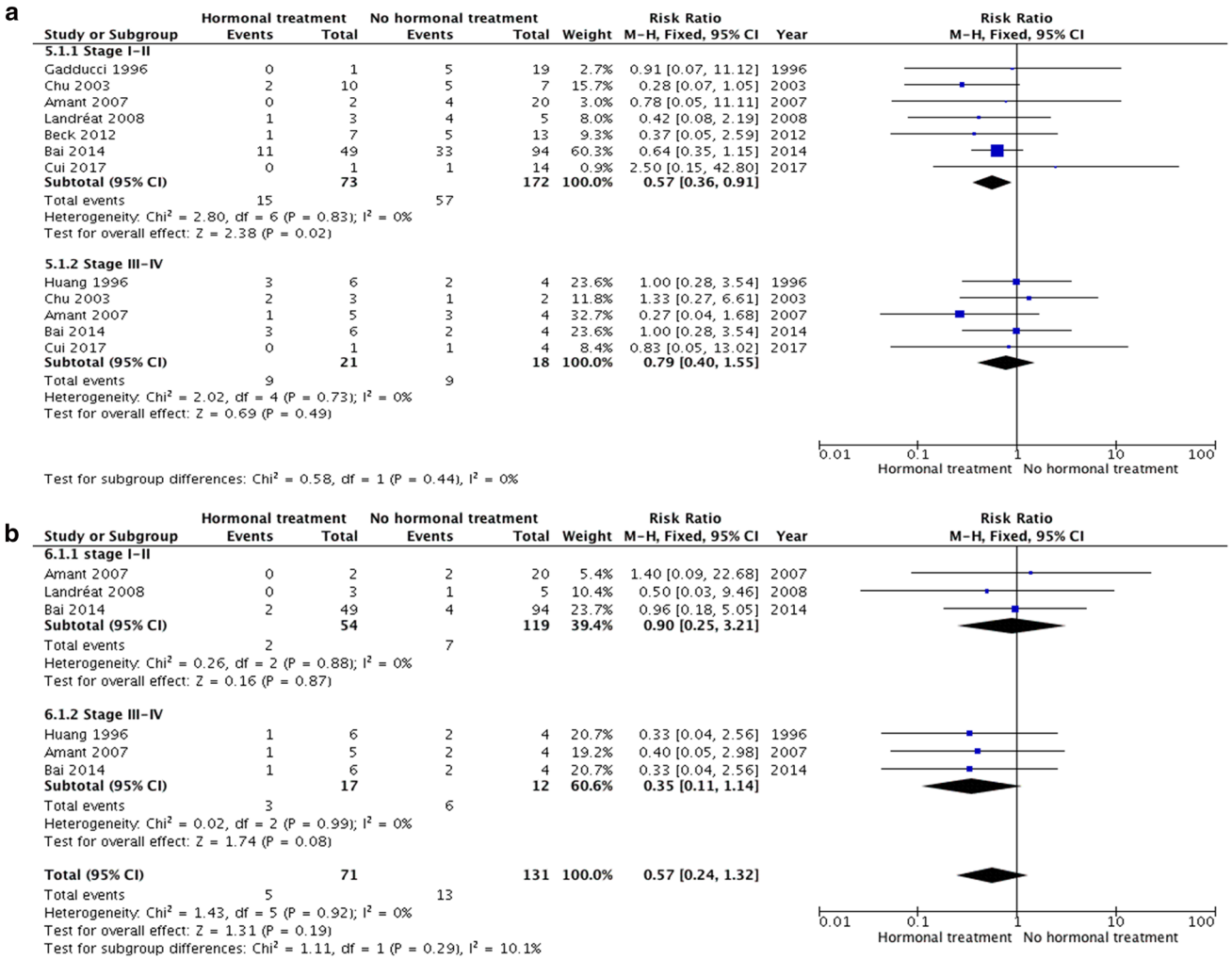

Fig. 4 Stratified analysis by FIGO stage. For the stage I–II patients, hormonal treatment could significantly decrease the risk of recurrence (RR = 0.57, 95% CI 0.36–0.91, $P = 0.02$) (**a**), but could not influence overall survival (RR = 0.90, 95% CI 0.25–3.21, $P = 0.87$) (**b**). For stage III–IV patients, hormonal treatment had little benefit both in reducing the recurrence risk and prolonging overall survival (RR = 0.79, 95% CI 0.40–1.55, $P = 0.49$/RR = 0.57, 95% CI 0.24–1.32, $P = 0.08$) (**a**, **b**)

adjuvant treatment should be performed or not. In clinical practice, chemotherapy, radiotherapy, and hormonal treatment had been used in LG-ESS patients, either alone or in combination. LG-ESS was poorly responsive to adjuvant chemotherapy due to a low mitotic index [16]. Adjuvant radiotherapy has never been shown to have clinical benefits for LG-ESS patients [2], but palliative radiotherapy could be used for recurrent or metastatic disease [23]. Overall, based on the clinical benefits and side effects, adjuvant hormonal treatment was the most recommended modality for LG-ESS patients, especially for patients with advanced and recurrent disease [2, 4, 23–25]. However, due to the rarity of LG-ESS and lack of consensus on surgical guidelines, available prospective data about the benefit of adjuvant hormonal treatment are limited and difficult to obtain especially RCT data. Current data for LG-ESS are mainly from retrospective series and case reports. Seagle et al. [15] reported a large retrospective cohort analysis including 2414 LG-ESS patients from the 1998 to 2013 National Cancer Database and investigated the prognostic information, which was the largest published series related to LG-ESS patients. The matched and unmatched cohort analysis results both indicated that adjuvant hormonal therapy had little benefit on overall survival. However, given that only 12.7% of LG-ESS patients received hormonal therapy, the authors suggested that it was not appropriate to interpret the negative result for an association of hormonal therapy with survival in LG-ESS as evidence for a lack of benefit. In addition, there were no data associated with the effect of hormonal treatment on the recurrence risk in the largest published cohort study. Some small retrospective studies also discussed the role of adjuvant hormonal treatment

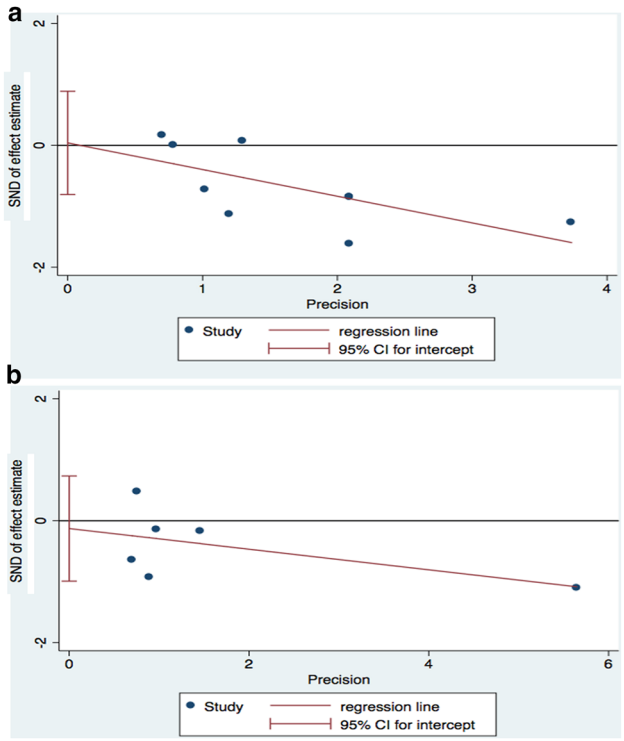

Fig. 5 Egger's publication bias plots. For analysis of recurrence (**a**, 9 studies) and death (**b**, 6 studies), Egger's publication bias plots showed that no publication bias existed among our included studies ($P = 0.912/0.700$)

for LG-ESS, while no consensus was reached [5, 10–14]. There are still not enough valid data to verify the benefit of adjuvant hormonal treatment for the prognosis of patients with LG-ESS. In addition, these negative or positive results should be interpreted cautiously because only a small percentage of patients received hormonal treatment in the majority of studies, and a treatment assignment bias that patients with advanced disease were selectively given adjuvant hormonal treatment alone or in combination with other treatment modalities should also be noted.

In the present study, 10 retrospective studies were pooled to demonstrate the role of hormonal treatment for LG-ESS. The pooled results indicated that hormonal treatment was effective at reducing the recurrence risk but had little effect on prolonging overall survival. Despite the indolent nature of LG-ESS, recurrences are not uncommon. Although the reported overall disease-specific 5-year and 10-year survival rates are 80–90% and 70%, respectively [21, 26], 23–59% of all LG-ESS patients suffered from recurrence [2]. Therefore, although LG-ESS has an indolent clinical course with a tendency for late recurrence, based on the meta-analysis results, we suggested that adjuvant hormonal treatment should be considered as a feasible adjuvant therapy for patients with LG-ESS.

However, some questions about hormonal treatment remain, including the optimal drug species (progestins, aromatase inhibitors or GnRH-a), doses, and duration of therapy. In the 10 included studies, progestin, aromatase inhibitors and GnRH-a were used in 6, 2 and 2 studies, respectively, except for 4 studies without detailed use of hormonal treatment.The optimal type of hormone was not discussed in other studies. Only 2 studies demonstrated that hormonal treatment was administered for 3–4 or 6 months [20, 21]. Some considered a 2-year duration of adjuvant hormonal treatment sufficient, and others believed that the treatment should be lifelong [23]. However, there was an absence of solid data to evaluate the feasibility and reasonability of the duration of therapy. Future clinical trials are needed to investigate how to perform adjuvant hormonal treatment reasonably.

Prognosis may be primarily associated with disease stage [2]. The median time to recurrence has been shown to be 5.4–9.3 years for stage I–II patients and only 9 months for stage III–IV patients [4, 24]. The reported overall disease-specific 5-year survival rates of stage I–II and stages III–IV patients are approximately 90% and 50%, respectively [4]. In addition, for LG-ESS patients, hormonal treatment could be used with chemotherapy, and/or radiotherapy, and for patients without hormonal treatment, chemotherapy, and/or radiotherapy was usually used. Although no substantial heterogeneity across these studies was detected both in the meta-analysis recurrence and death (both $I^2 = 0\%$), we still performed stratified analysis to reduce heterogeneity deriving from FIGO stage and other adjuvant treatment modalities. The pooled results in the present meta-analysis showed that hormonal treatment alone could significantly decrease the risk of recurrence compared with the risk in the group without any adjuvant treatments. For patients with early-stage disease, hormonal treatment was effective at reducing the risk of recurrence. However, the negatively prognostic survival associations of adjuvant hormonal treatment were obtained for stage III–IV patients. Adjuvant hormonal treatment was usually recommended for patients with advanced-stage or recurrent disease, but for patients with early-stage disease, the value of hormonal treatment remained unproven in the literature [2, 13]. The small sample size of studies and poor prognosis of patients with advanced-stage disease might be the main causes of inconsistent results. The feasibility of hormonal treatment for patients with different FIGO stages needs to be further evaluated.

In addition to the patients' prognosis being affected by the FIGO stage and other adjuvant treatments, including chemotherapy and radiotherapy, the different types of hormonal treatment (progestins, GhRH-a, and aromatase inhibitors) may have different effects on the clinical benefits. However, there is little information about the different type of hormonal treatment. No studies included in this meta-analysis

reported the prognosis of patients with the different types of hormonal treatment. In addition, the adverse drug reactions of hormonal treatment were not reported in detail in the included studies. A retrospective study [13] which was excluded from this meta-analysis based on exclusion criteria, indicated that aromatase inhibitor and was better tolerated than progestins. In addition, 79% stage I patients taking megestrol acetate reduced or stopped taking the progestin because of unacceptable side effects [13]. However, the unacceptable side effects were not reported in detail. Therefore, more future studies are needed to compare the clinical benefits of different types of hormonal treatment and the toxicity of hormonal treatment.

The major limitation of this meta-analysis was the selection bias for hormonal treatment prescription in the included studies with a retrospective study design. In addition, considering the retrospective study design among studies, potential publication bias and a limited number of included studies, the pooled results still need to be interpreted cautiously. Despite all of these limitations, the present study provided insight into the adjuvant treatment of LG-ESS patients. Future studies exploring the role of adjuvant hormonal treatment for LG-ESS patients are needed to verify our results, especially multicenter prospective studies.

In conclusion, based on currently available evidence, the pooled results of this meta-analysis suggest that adjuvant hormonal treatment should be considered as a feasible adjuvant therapy for reducing the recurrence risk of patients with LG-ESS while bearing little benefit on overall survival.

Authors' contribution: The present study is contributed by Ran Cui, Guangming Cao, Huimin Bai, and Zhenyu Zhang. RC: data collection and analysis, manuscript writing; GMC: data collection and analysis, HMB and ZYZ: protocol development, data management and analysis, and manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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