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Original Article

The feasibility of fertility-sparing surgery in treating advanced-stage borderline ovarian tumors: A meta-analysis

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ABSTRACT

Objective: To evaluate the feasibility of fertility-sparing surgery in treating advanced-stage borderline ovarian tumors (BOTs).

Materials and methods: The databases of PubMed, Cochrane Library, EMbase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Weipu (Chinese), and Wanfang (Chinese) were searched using the keywords "advanced-stage borderline ovarian tumors", "fertility-sparing surgery", "conservative surgery", and "borderline ovarian tumor" to collect the clinical controlled trails (CCTs) regarding fertility-sparing surgery for the treatment of advanced-stage BOT. The references of those CCTs were also searched manually. Data extraction and quality assessment were done using Review manager Version 5.1 and R software Version 2.11.1.

Results: Four studies involving 74 patients were included. The results of meta-analysis showed that: (1) compared with radical surgery, the recurrence of the fertility-sparing surgery during the follow time is higher with significant difference [odds ratio (OR) = 3.87, 95% confidence interval (CI) (1.20,12.44), $p = 0.02$]; (2) the difference of survival rate between the two groups was not significant [5-year survival: OR = 0.85, 95%CI (0.03, 23.82), $p = 0.92$; 7-year survival: OR = 0.80, 95%CI (0.08, 8.41), $p = 0.85$]; and (3) concerning fertility results in fertility-sparing surgery, 18 patients tried to become pregnant, 15 pregnancies were achieved in the 11 patients, 11 full-term deliveries.

Conclusion: The rate of ovarian recurrence in patients who underwent conservative treatment was higher than in patients with radical treatment, but it did not affect patient survival; fertility-sparing surgery could be induced to preserve the fertility potential of young patients.

Introduction

Borderline ovarian tumors (BOTs), first described in 1929 [1], constitute approximately 10–15% of all epithelial ovarian malignancies. BOTs, which are recognized as a separate diagnostic category of epithelial ovarian tumors, are characterized pathologically by features of malignant tumors, including cellular proliferation, stratification of the epithelial lining of the papillae, nuclear atypia, and mitotic activity, but without destructive stromal invasion [2]. Clinically, BOTs are detected at earlier stages and younger age at diagnosis, have more indolent behavior, longer survival, and later recurrence compared with invasive ovarian cancer [3]. Although the majority of BOTs are found in the early stages, approximately 20% still present in advanced stages (Stages II–IV) at the time of diagnosis [4]. Stage II or Stage III was defined as the presence of a BOT in addition to pelvic (Stage II) and/or abdominal (Stage III) peritoneal implants. Surgery is the most important treatment for BOTs, including fertility-sparing surgery, radical surgery, and complete surgical staging. Fertility-sparing surgery was defined as a procedure with preservation of the uterus and at least part of one ovary, which include four types: unilateral adnexectomy (UA), UA + contralateral cystectomy (UA + CC), unilateral cystectomy (UC), and bilateral cystectomy (BC). Fertility-sparing surgery for early-stage BOTs is accepted as a valuable alternative in a number of young patients who want to preserve their fertility [3,5]. In recent years, very few studies reported the fertility outcome of conservative management in patients with advanced-stage BOTs. However, the prognosis of patients with invasive implants is much poorer [6], such patients with conservative surgery are not usually

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recommended. Therefore, the safety of conservative management is still unclear in young patients with advanced-stage disease [7].

This study aimed to evaluate the safety and effectiveness of fertility-sparing surgery in treating advanced-stage BOTs.

Materials and methods

Search strategy and selection criteria

We sought data from published articles which were compared with the clinical results between conservative surgery and radical surgery by electric and manual searching. We followed the guideline of MOOSE [8] (Meta-analysis of Observational Studies in Epidemiology) and the recommendations of Cochrane handbook Version 5.1.0 [9] to systematically conduct and report this meta-analysis.

We searched from May 2001 to April 2014 using electronic databases. Electronic database searching included PubMed, Cochrane Library, EMbase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), VIP (Chinese), and Wanfang (Chinese). The keywords used were "advanced-stage borderline ovarian tumors", "fertility-sparing surgery", "conservative surgery", and "borderline ovarian tumor". Over the same period, we also manually searched using the references cited in the acquired articles. No language restrictions were made. In addition, we searched related magazines.

The eligibility criteria applied was the following: (1) confirmed by clinical pathology with advanced BOT; (2) did not receive preoperative chemotherapy; (3) compared conservative surgery with radical surgery; (4) report on at least one of the outcome measures which include reproduction outcomes, recurrent rate, and survival rate. Articles were excluded from the analysis if: (1) confirmed by pathology with the other ovarian tumor; (2) the clear follow-up results were not mentioned; (3) the outcomes were not clearly reported; (4) they were without a control group; (5) it was impossible to extract data from the study; and (6) they are repeat published literature.

Study selection

Two reviewers reviewed all potential studies and accessed them using a three-step processes. Firstly, they independently reviewed the titles and abstracts of all potential studies to exclude duplications. Secondly, they examined the studies by title, abstract, and full text to assess whether the studies ought to be included or excluded. Thirdly, they accessed the studies using qualitative synthesis. When the judgments of two reviewers had differences, a further discussion would be presented to solve the problem.

Quality assessment

We assessed the quality of individual studies using the Newcastle–Ottawa Scale. Specifically, the Newcastle–Ottawa Scale in the methods indicates cases independently validated, representativeness of the cases, selection of controls, definition of controls, comparability, ascertainment of exposure by blinded interview or record, same method of ascertainment used for cases and controls, and nonresponse rate the same for cases and controls.

Statistical analysis

Analysis was performed using the statistical software Review Manager Version 5.1 and R software Version 2.11.1 [10]. Heterogeneity was evaluated using the χ^2 test, $p \leq 0.05$ was considered significant for heterogeneity. If heterogeneity with $p > 0.05$, $I^2 < 50\%$ was present, the fixed effects model was used. If heterogeneity with $p \leq 0.05$, $I^2 \leq 50\%$ was present, the random effects model was used. If heterogeneity with $p \leq 0.05$, $I^2 \geq 50\%$ was shown, a sensitivity analysis was performed. The sensitivity analysis was conducted using R software (Version 2.11.1, package meta) [10].

Dichotomous variables were analyzed using odds ratio (OR) and 95% confidence interval (CI), and continuous variables were represented using mean difference and 95% CI. When there were no events in one group, it would be solved by adding 0.5 to each cell of the 2×2 table [11]. In addition, if there were no events for both groups, the study was excluded. If the clinical trial data could not be incorporated into the analysis, the descriptive analysis was used. Publication bias was represented by funnel plots and was further assessed using R software (Version 2.11.1, package meta) [10].

Results

Search results

A total of 48 relevant studies were identified for initial review. Twenty original studies were excluded for duplicates. By reviewing the titles and abstracts [4,7,12–37], 14 of the original studies were excluded for not having a control group [4,7,12–23]. Then the full text of the remaining studies were reviewed, seven studies were excluded because they did not provide sufficient information [24–30], and three articles were eliminated because the criteria of case selection were not the same [31–33]. Finally, four studies were included in the analysis (Figure 1) [34–37].

The characteristics of the included studies are shown in Table 1, and ratings of study quality for each of the Newcastle–Ottawa criteria [38] are presented in Table 2. Overall, four relevant studies were identified. The total analysis population was 74, 35 of which were in fertility-sparing surgery, and 39 in radical surgery. In summary, the quality of each publication's score was high. A higher score represented a better methodological quality.

Meta-analysis

All of the four studies reported recurrence rates. There was no evidence of heterogeneity among these studies ($p = 0.57$, $I^2 = 0\%$). Therefore, fixed effects model was used. Figure 2 shows the forest plots for recurrence rate. The results showed that fertility-sparing surgery achieved significantly higher recurrence rate [OR = 5.58, 95%CI (1.66, 18.78), $p = 0.005$].

Three studies [34–36] reported survival rate. There was no evidence of heterogeneity among these studies ($p = 0.96$, $I^2 = 0\%$). Fixed effects model was used. Figure 3 shows the forest plots for 5-year survival rate, and Figure 4 for 7-year survival rate. The results were shown without significant difference [5-year survival: OR = 0.85, 95%CI (0.03, 23.82), $p = 0.92$; 7-year survival: OR = 0.80, 95%CI (0.08, 8.41), $p = 0.85$].

Three studies [35–37] reported reproductive outcome. Song et al [35] reported that four patients had attempted to conceive, four healthy term babies had been born without congenital anomalies, and one woman was in the second trimester of pregnancy. Kane et al [36] presented that seven pregnancies were achieved in the five patients—five full-term deliveries, one ectopic pregnancy, and one spontaneous abortion. Deffieux et al [37] reported five patients tried to become pregnant, and three spontaneous pregnancies were observed in two patients.

Sensitivity analysis and subgroup analysis

A sensitivity analysis was performed using the random effects model and inverse variance method to detect the stability of these

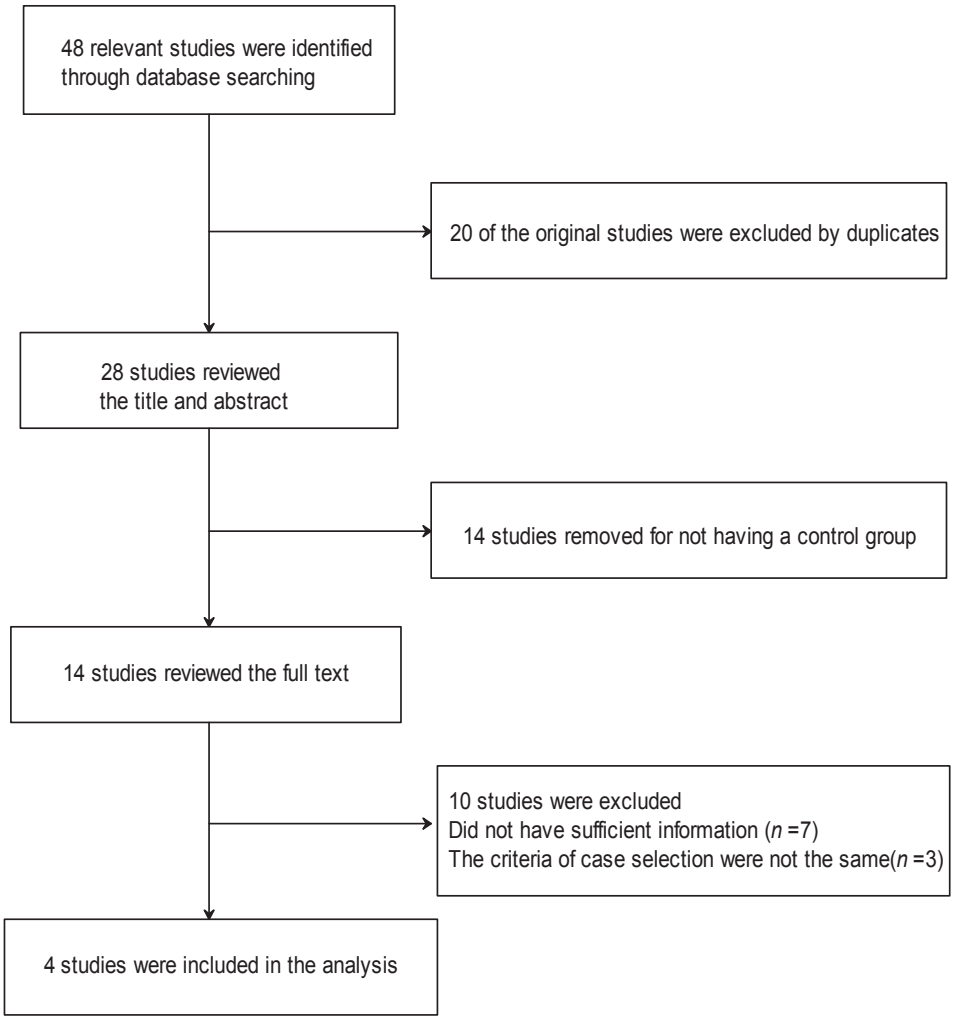


Figure 1. Flow diagram of search strategy.

Table 1
Characteristics of included studies.

Study	Age (y), mean		Cases		Follow up (mo)	Histological type (cases)		Outcomes
	Conservative group	Radical group	Conservative group	Radical group		Conservative group	Radical group	
Viganò et al [34]	36	49	10	12	91	S = 10 N = 0	S = 12 N = 0	A;B;C
Song et al [35]	32	48	5	20	71.4	S = 4 N = 1	S = 16 N = 4	A;B;C;D
Kane et al [36]	25.9	45.8	13	5	38	S = 10 N = 0	S = 10 N = 0	A;B;C;D
Deffieux et al [37]	22.3	50.5	7	2	35	S = 10 N = 0	S = 10 N = 0	A;D

A = recurrent rate; B = 5-year survival rate; C = 7-year survival rate; D = reproduction outcomes; N = mucinous tumor; S = serous tumor.

results, while alternating analytical models, similar results were obtained (Table 3). The sensitivity analysis showed that the results were relatively stable.

As BOTs could be divided into six categories according to their histopathology, but were mainly divided into serous and mucinous types, we, therefore, conducted subgroup analysis for serous or mucinous categories. To stay in line with previous analyses, the subgroup analyses were also performed for recurrence rate, 5-year survival, and 7-year survival (Figures 5–7).The results were similar to previous analyses. Especially, for the serous type of borderline tumor, the results showed that fertility-sparing surgery achieved significantly higher recurrence rate but without significant difference in the 5-year survival rate or 7-year survival rate. For the mucinous borderline tumor, the results remain the same.

Discussion

This study performed a meta-analysis to evaluate the feasibility of fertility-sparing surgery in treating advanced-stage BOTs. Only four studies met the inclusion and exclusion criteria and all were of small to a small size. However, each publication represented a better methodological quality than other studies. In addition, the sensitivity analysis indicated that the results were relatively stable.

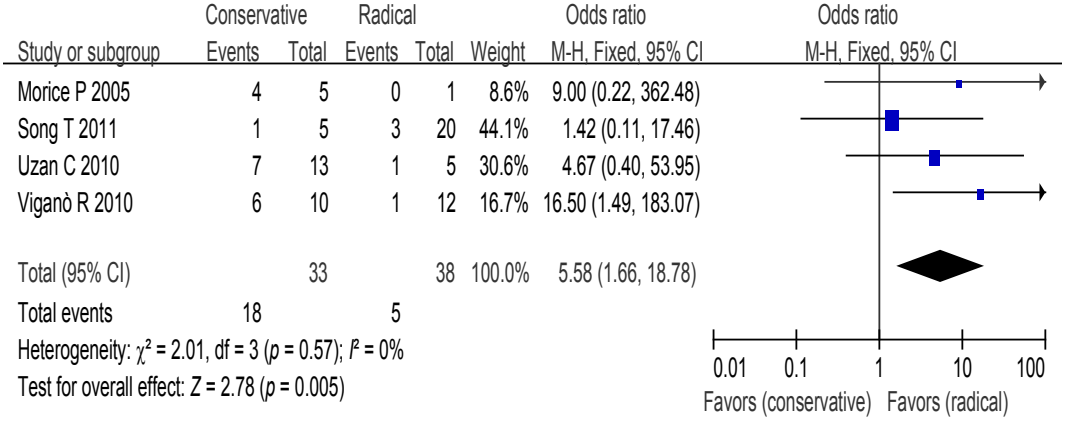
Table 2
Assessment of study quality.

Studies	Quality indicators from Newcastle–Ottawa Scale[a]							
	1	2	3	4	5	6	7	8
Viganò et al [34]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Song et al [35]	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Kane et al [36]	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Deffieux et al [37]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

[a] For the studies: 1, indicates cases independently validated; 2, representativeness of the cases; 3, community controls; 4, controls that have radical surgery; 5, comparability, 6, ascertainment of exposure by blinded interview or record; 7, same method of ascertainment used for cases and controls; 8, nonresponse rate the same for cases and controls.

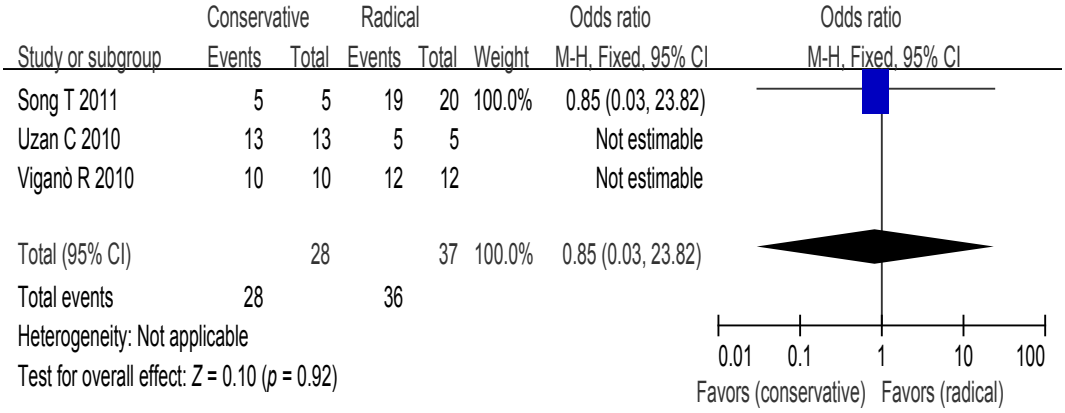
The present meta-analysis of four observational studies shows that whether it is serous or mucinous tumor type, the rate of recurrence in patients who have conservative treatment is higher than in those who have radical treatment. However, such management does not affect survival. There have been many studies indicating their excellent long-term prognosis [39]. The 10-year survival rate is: 99% for Stage I, 98% for Stage II, 96% for Stage III, and 77% for Stage IV [4,40]. Laurent et al [13] reported cases in patients who were treated conservatively with serous BOT with stromal microinvasion but without micropapillary pattern, most patients who had recurrence of disease following conservative treatment had borderline tumor, and such recurrence can be easily cured using a surgical approach. Camatte et al [12] reported 17 cases in patients with advanced-stage disease: two patients relapsed, no patient died. Song and Kong [41] also reported similar results. In the recent paper by Uzan et al [7] including 11 BOTs with invasive implants, eight relapsed, two of whom had invasive carcinoma. According to the literature, the most important prognostic factor of patients with advanced-stage BOT is the histologic characteristics of the implants (noninvasive or invasive), and the prognosis of patients with invasive implants is much poorer. Therefore, the higher risk of relapse can be accepted because of the good prognosis and the role of a second surgery. Fertility-sparing surgery in the case of a patient with advanced-stage BOT should be considered if she does not have tumors with invasive implants.

In our series, the reproductive outcomes were less reported. Our study reports 15 pregnancies in 11 patients treated conservatively, and 13 healthy term babies were born. Our results confirm that fertility outcome is good, following conservative treatment of advanced stage BOT. In the recent series by Uzan et al [7], the pregnancy rate was 57.1% according to long-term follow up. Camatte et al [12] also reported similar results. These results



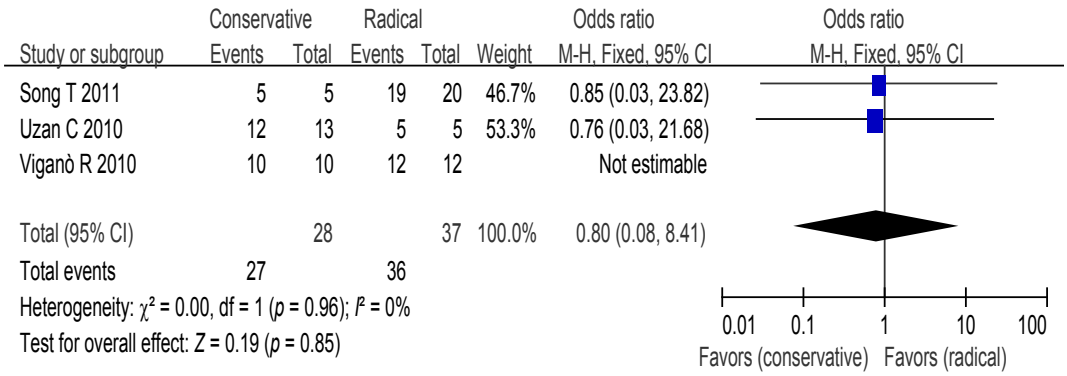
CI = confidence interval.

Figure 2. Forest plot for recurrence rate.



CI = confidence interval.

Figure 3. Forest plot for 5-year survival rate.



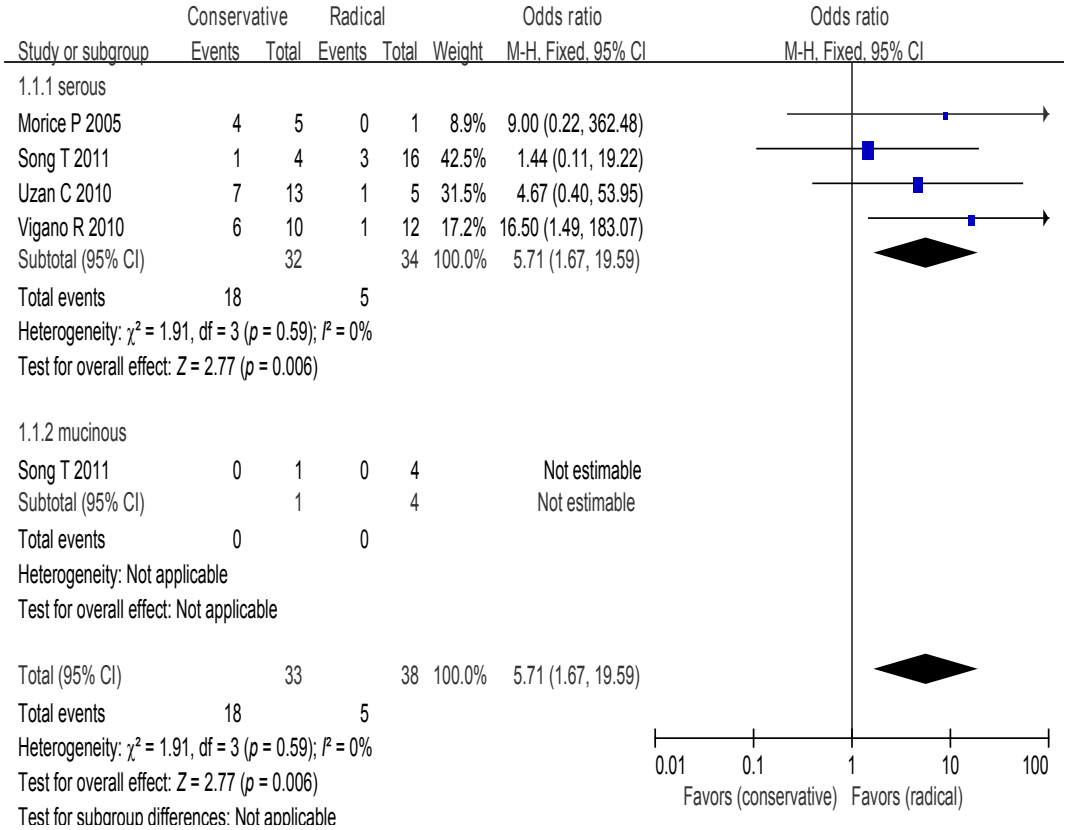
CI = confidence interval.

Figure 4. Forest plot for 7-year survival rate.

Table 3
Sensitivity analysis with alternating analytical models.

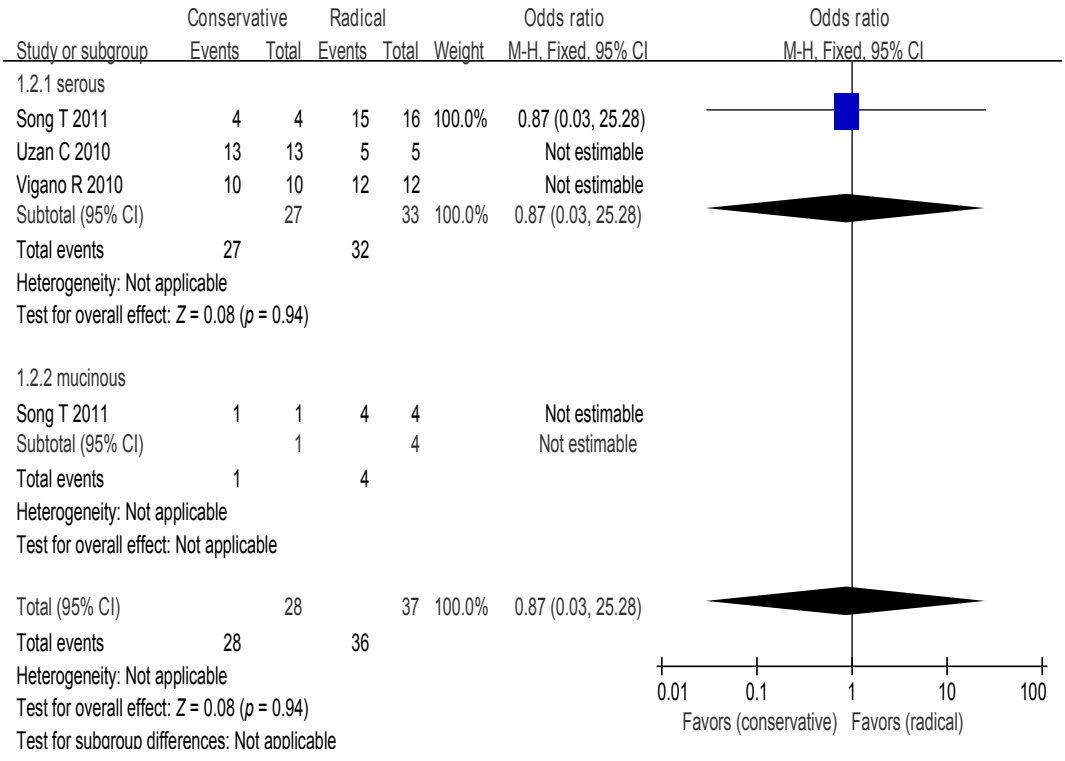
	Fixed effects model				Random effects model			
	OR	95%CI	*p*	I^2 (%)	OR	95%CI	*p*	I^2 (%)
Recurrence rate	5.58	(1.66, 18.78)	0.005	0	5.34	(1.42, 20.06)	0.01	0
5-year survival	0.85	(0.03, 28.82)	0.92	0	0.85	(0.03, 28.82)	0.92	0
7-year survival	0.80	(0.08, 8.41)	0.85	0	0.80	(0.08, 8.53)	0.85	0

CI = confidence interval; OR = odds ratio.



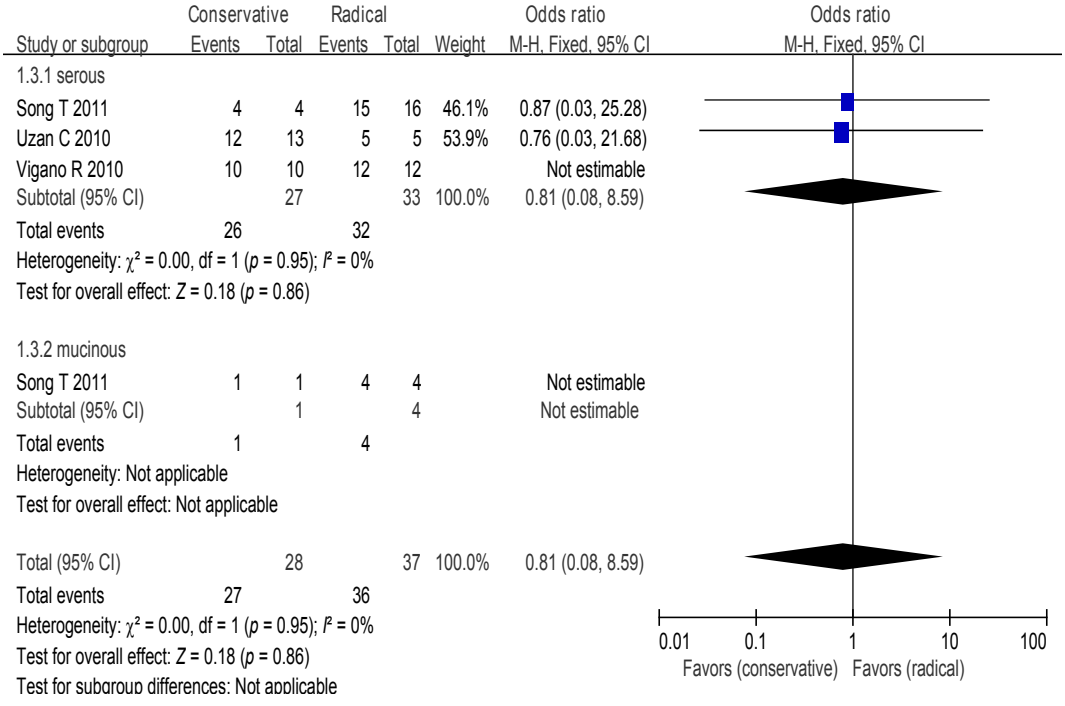
CI = confidence interval.

Figure 5. Subgroup forest plot of recurrence rate.



CI = confidence interval.

Figure 6. Subgroup forest plot of 5-year survival.



CI = confidence interval.

Figure 7. Subgroup forest plot of 7-year survival.

indicate that reproductive outcomes after fertility-sparing surgery, even if the patient had an advanced-stage BOT, are very promising.

This study has several limitations: (1) only four studies met the inclusion criteria, all of which were of small size. It was greatly underpowered to draw any conclusions. Our results showed that fertility-sparing surgery in the case of a patient with advanced-stage BOT should be considered, but these results had not been demonstrated for a large enough number of; (2) all included studies were of retrospective design, therefore possibly introducing some degree of bias; (3) all the included studies were published in English, the present meta-analysis was limited by language bias. Moreover, we did not search for unpublished studies, and therefore the study might be limited by publication bias; (4) there were only four outcomes, such as recurrence, 5-year survival, 7-year survival and pregnancy, reported in our study, which is not enough to determine the feasibility. Therefore, more outcomes are needed for further study; and (5) the conclusion we made is not significantly different from those of previous articles, it indicates the research progress of BOT is rather complex, and more research is needed.

Conclusion

In conclusion, fertility-sparing surgery achieves a higher recurrence rate. However, it does not affect survival, and reproductive outcomes are promising. However, more well-designed clinical trials are needed to determine the feasibility of fertility-sparing surgery in treating advanced-stage BOT with different pathological types.

Conflicts of interest

All authors have no conflicts of interest to declare.

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