Research Article

Prognosis and Prognostic Factors of Serous Borderline Tumor-Micropapillary Variant: Retrospective Study of 200 Patients with Long-Term Follow-Up

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Objective. To determine the oncofertility outcomes and prognostic factors in a large series of serous borderline ovarian tumor-micropapillary variant (SBOT-M) with a long-term follow-up. Methods. Consecutive patients with SBOT-Ms treated from two affiliated hospitals of the Chinese Academy of Medical Sciences were retrospectively reviewed. Prognostic factors on invasive recurrence, disease-free survival (DFS), and overall survival were analyzed, and outcomes of patients treated with conservative and radical surgery were compared. Results. From 2000 to 2020, 200 patients were identified and followed. After a median follow-up of 68 months, 81 patients relapsed. In the multivariate analyses, younger age at diagnosis and conservative surgery that preserved fertility potential were independently associated with worse DFS (p = 0.018 and < 0.001, respectively). Twenty-three patients experienced invasive recurrence, and seven died of progressive disease. Multivariate analysis showed that nulliparous and advanced FIGO stage were independently adversely associated with lethal recurrence (p = 0.022 and 0.029, respectively). Only advanced FIGO stage at diagnosis was associated with worse overall survival at univariate analysis (p = 0.02). Among 61 patients attempting conception, 37 achieved 44 pregnancies and resulted in 32 live births. Conclusions. In this series, patients with SBOT-M have an acceptable oncofertility outcomes. The use of conservative surgery was independently associated with worse DFS, but without an impact on neither invasive relapse nor on overall survival. Patients with advanced FIGO stages had a significantly higher risk of lethal recurrence and worse overall survival, suggesting that adequate staging surgery and intensive postoperative surveillance should be warranted.

1. Introduction

Serous borderline ovarian tumor-micropapillary variant (SBOT-M, also referred to as noninvasive low-grade serous carcinoma), the aggressive variant of SBOTs, makes up approximately one-quarter of all cases of SBOTs [1–5]. It was first described by Burks et al. [6] and Seidman and Kurman [7] in 1996 and is characterized by SBOTs with nonhierarchical branching architecture featuring micropapillary and/or cribriform patterns [8]. Compared to their typical counterparts, patients with SBOT-Ms are more commonly associated with extraovarian implant (particularly invasive
implants), the presence of bilateral disease and areas of microinvasion, increased tumor recurrence, and higher mortality [9–11].

Given its recent introduction and specific features, however, very few data have specifically addressed the prognosis and feasibility of fertility preservation in patients with SBOT-Ms. Most available studies have focused mainly on the prognostic impact of the micropapillary pattern on SBOTs and documented poor disease-free survival (DFS) and high invasive evolution risk for women with SBOT-Ms [3, 4, 10–16]. Nevertheless, given the higher rate of concomitant extraperitoneal disease in SBOT-Ms, whether this risk is due to the intrinsic biology of micropapillary pattern or to the coexisting implants continues to fuel debate. In patients with advanced-stage disease, several studies have reported similar prognosis in SBOT with and without a micropapillary pattern [11, 15–19]. On the contrary, in the pooled analyses by Vasconcelos et al., patients with SBOT-Ms (regardless of stage) have a significantly higher rate of lethal recurrence than patients with advanced-stage SBOTs (implants of any type, regardless of the presence of SBOT-Ms or not) [5]. Regarding reproductive outcomes, only two retrospective series with small sample sizes (n = 8 and 15, retrospectively) have been published [17, 20].

Thus, the objective of current series was to describe the clinical characteristics and outcomes of patients with SBOT-Ms and to evaluate the safety of conservative surgery in selected patients. To our knowledge, this is the most extensive series of patients with SBOT-Ms that specifically dedicated to determine their prognostic factors with an extended follow-up.

2. Materials and Methods

2.1. Study Population. Consecutive patients with SBOT-Ms treated between January 2000 and June 2020 were identified retrospectively from two affiliated hospitals of the Chinese Academy of Medical Sciences. Data on demographics, clinicopathological findings, follow-up information, and fertility outcomes were retrieved from medical records or by telephone interview. Patients who were lost to follow-up within six months after initial surgeries were excluded. Institutional Review Board approval was obtained at both institutions, and verbal informed consent was obtained during follow-up visits or telephone interviews.

Pathology slides were reviewed by an experienced pathologist from each institution according to the 2014 WHO classification [8], and no centralized pathological review has been performed. When there was disagreement, the slides were rereviewed, and a consensus was reached via a discussion. SBOT-M is defined as SBOT with nonhierarchical branching papillae featuring either elongated filiform “micropapillae” (≥ 5 : 1 length to width ratio) or cribriform epithelial lining the cyst walls [6–8]. We classified extraovarian peritoneal implants as noninvasive or invasive based on the absence or presence of destructive stromal invasion of the underlying tissues [1, 21]. Ovarian tumors with stromal microinvasion were defined as the presence of stromal infiltration <10mm² or <5 mm. Surgical stage was determined using the 2014 FIGO classification system for ovarian cancer based on surgical and pathological findings [22].

2.2. Treatments and Follow-Up. The surgical treatment modality was determined after discussion with the individual based on the disease extent, the surgical teams, age of the patient, and fertility-preservation desire. Surgery consisted of either radical (bilateral salpingo-oophorectomy with or without hysterectomy) or conservative treatment (defined as salvage of the uterus and at least parts of one ovary). Staging quality was considered comprehensive when all peritoneal surfaces were carefully explored by cytology, random or oriented multiple biopsies, and omentectomy [23]. Adjuvant chemotherapy was decided by the treating physicians based on the pathological findings and date of the treatment.

Patients were followed up with a pelvic examination, ultrasound scan, and CA-125 evaluation every three months during the first year after surgery, then every six months for two years, and yearly thereafter.

2.3. Statistical Analyses. Two end-points were retained for the statistical analysis: (1) the rate of recurrence (purely borderline recurrence and as collective invasive disease) and (2) the rate of invasive recurrence in the form of invasive adenocarcinoma or invasive implants during follow-up [11, 14–16, 19, 24–26]. All recurrence was diagnosed radiographically or clinically and confirmed histologically. Disease-free survival (DFS) was calculated from the date of surgery to the date of first recurrence or the last follow-up. And invasive DFS was calculated as the interval from surgery to invasive recurrence (recurrence in the form of invasive adenocarcinoma or invasive implants) or last follow-up. Given the relatively indolent behaviors of SBOT-Ms and low-grade serous carcinoma, we defined overall survival (OS) as a secondary outcome, which was measured from surgery to disease-related death or last contact [14, 15, 19]. Survival analyses were conducted using the Kaplan–Meier method and compared with the log-rank test, and a Cox regression model with forward stepwise selection was used for multivariate analyses, including prognostic factors that were statistically significant in the univariate analysis. Concerning fertility outcomes, we defined pregnancy as visualization of a gestational sac with positive serum β-HCG levels. All statistical analyses were performed using SPSS 25.0 and GraphPad Prism 5.0, and a p value of <0.05 was considered significant.

3. Results

3.1. Patient Characteristics. During the study period, 222 patients with SBOT-Ms were identified, and 22 were excluded due to the lack of sufficient follow-up. Among 200 patients included in the current analysis, 122 had undergone conservative surgery, and 78 received radical therapy during their management. The demographics and tumor characteristics of the study cohort stratified by treatment modality are summarized and compared in Table 1.

The median age at the time of diagnosis was 32 years (range, 17–68 years), and patients who underwent conservative surgery were significantly younger and more likely to be nulliparous than those in the radical surgery group (p < 0.001 and <0.001, respectively). Two-thirds of the tumors were resected with the open approach (67.0%, n = 134/200) during their initial
therapies, and complete staging surgery was performed in 127 patients (63.5%). After surgery, 54 patients (27.0%) received multiple different platinum-based chemotherapies due to extra-ovarian implants (20 invasive and 23 noninvasive), stromal microinvasion (n = 3), or unspecified reasons managed outside our hospitals (n = 8). The proportions of laparotomy approach, complete staging, and postoperative chemotherapy were significantly higher in the radical group (p < 0.001, <0.001, and <0.001, respectively).

Regarding pathological features, 137 patients (68.5%) had bilateral ovarian involvement, and 94 (47.0%) had extra-ovarian implants, including invasive and noninvasive implants, in 26 (13.0%) and 68 (34.0%) of affected patients, respectively. The proportions of patients with bilateral ovarian involvement (62.3% versus 78.2%, p = 0.018) and extra-ovarian implants (36.1% versus 64.1%, p < 0.001) were significantly lower in the conservative group.

3.2. Oncological Outcomes. After a median follow-up of 68 months (range, 6-240 months), 81 patients (40.5%) recurred in a delay from 3 to 140 months after their initial surgeries, including 73 (n = 73/122, 59.8%) in the conservative group and 8 (n = 8/78, 10.3%) in the radical group. Table 2 shows the characteristics of patients with recurrence. Of the 81 patients with relapse, 72 were borderline at first recurrences, 34 had 2nd recurrences, and 13 experienced 3rd to 5th recurrences. In the radical group, the most common sites of recurrence were the peritoneum seeding (n = 4) and with bowel involvement (n = 4). In the conservative group, however, the most common sites of recurrence were the isolated ovary/ovaries (n = 47) and with peritoneal seeding (n = 26). Of these, 50 patients were salvaged with further conservative surgery.

The results of univariate analysis on DFS are summarized in Table 2. Univariate analysis of our data demonstrated that aged ≤ 35 years, nulliparous, incomplete staging surgery, not underwent lymphadenectomy, and conservative surgical extent (Figure 1(a)) were significantly associated with poorer DFS (p < 0.001, <0.001, =0.015, <0.001, and <0.001, respectively). As shown in Table 2, none of the pathological features was associated with DFS. After multivariate analysis, the use of conservative surgery and younger age at diagnosis was significantly associated with worse DFS (conservative versus radical, HR: 5.8, 95% CI: 2.6-12.8, p < 0.001; age ≤ 35 years versus >35 years, HR: 2.4, 95% CI: 1.2-4.9, p = 0.018, respectively).

Of the 81 patients with relapse, 23 (28.4%) developed invasive disease in a delay from 3 to 106 months after their

| Parameters                          | Overall cohort, n (%) | Radical group, n (%) | Conservative group, n (%) | p value |
|-------------------------------------|-----------------------|----------------------|---------------------------|---------|
| Age (median, range, years)          | 32 (17-68)            | 42 (20-68)           | 28 (17-42)                | <.001   |
| Age, years †                        | ≤ 35                  | 125 (62.5)           | 22 (28.2)                 | <.001   |
|                                     | > 35                  | 75 (37.5)            | 56 (71.8)                 | 19 (15.6)             |
| Nulliparous                         | Yes                   | 108 (54.0)           | 20 (25.6)                 | <.001   |
|                                     | No                    | 92 (46.0)            | 58 (74.4)                 | 34 (27.9)             |
| CA-125 (median, range, U/mL)        | 210 (5.6-25000.0)     | 284.3 (5.6-25000.0)  | 175 (7.1-12313)           | .346    |
| Referral                            | Yes                   | 64 (32.0)            | 21 (26.9)                 | 43 (35.2)           | .218    |
|                                     | No                    | 136 (68.0)           | 57 (73.1)                 | 79 (64.8)           |
| Surgical approach                   | Laparotomy            | 134 (67.0)           | 69 (88.5)                 | 65 (53.3)           | <.001   |
|                                     | Laparoscopy            | 66 (33.0)            | 9 (11.5)                  | 57 (46.7)           |
| Complete staging                    | Yes                   | 127 (63.5)           | 74 (94.9)                 | 53 (43.4)           | <.001   |
|                                     | No                    | 73 (36.5)            | 4 (5.1)                   | 69 (56.6)           |
|                                     | No                    | 140 (70.0)           | 30 (38.5)                 | 110 (90.2)           | <.001   |
| Ovarian involvement                 | Unilateral            | 63 (31.5)            | 17 (21.8)                 | 46 (37.7)           | .018    |
|                                     | Bilateral             | 137 (68.5)           | 61 (78.2)                 | 76 (62.3)           |
| FIGO stage                          | I                     | 106 (53.0)           | 28 (35.9)                 | 78 (63.9)           | <.001   |
|                                     | II-IV                 | 94 (47.0)            | 50 (64.1)                 | 44 (36.1)           |
| Stromal microinvasion               | Yes                   | 164 (82.0)           | 55 (70.5)                 | 109 (89.3)           | .001    |
|                                     | No                    | 36 (18.0)            | 23 (29.5)                 | 13 (10.7)           |
| Type of implants (n = 94)           | Noninvasive           | 68 (72.3)            | 34 (68.0)                 | 34 (77.3)           | .316    |
|                                     | Invasive              | 26 (27.7)            | 16 (32.0)                 | 10 (22.7)           |
|                                     | No                    | 146 (73.0)           | 42 (46.2)                 | 104 (85.2)           | <.001   |
| Adjuvant chemotherapy               | Yes                   | 54 (27.0)            | 36 (53.8)                 | 18 (14.8)           |

Values are n (%) unless stated otherwise. †Based on X-tile analysis.
initial surgeries, including 16 (n = 16/122, 13.1%) in the conservative group and seven (n = 7/78, 9.0%) in the radical group. Of these cases, 14 relapsed as low-grade serous carcinoma (LGSC), and nine recurred as invasive peritoneal disease. The 5-year invasive DFS rates in the conservative and radical surgery groups were 88% and 90%, respectively (p = 0.452) (Figure 1(b)). Univariate analysis showed that nulliparous, bilateral ovarian involvement, and advanced FIGO stage (Figure 1(e)) were significantly associated with the risk of invasive DFS (p = 0.009, 0.015, and 0.014, respectively), and multivariable analysis found that nulliparous and advanced FIGO stage were independently associated with the invasive evolution of the disease (nulliparous versus parous, HR: 3.5, 95% CI: 1.2-10.4, p = 0.022; advanced versus early stage, HR: 1.6, 95% CI: 1.1-2.6, p = 0.029, respectively) (Table 3). Patients with noninvasive and invasive implants showed similar invasive DFS (p = 0.66). Notably, among 36 patients with advanced-stage disease experiencing relapse, 44% (n = 16) were diagnosed with invasive recurrence. On the other hand, among 45 patients with stage I disease experiencing recurrence, one seven (16%) developed lethal recurrence.

At the time of analysis, seven patients (3.5%) had died of their disease at a range of 37 to 158 months following primary surgeries, including four (n = 4/122, 3.3%) in the conservative group and three (n = 3/78, 3.8%) in the radical group. The 5-year overall survival rates in the conservative and radical surgery groups were 97% and 97%, respectively. No significant difference in overall survival was found between different treatment modalities (p = 0.542) (Figure 1(c)). As shown in Table 4, only advanced FIGO stage at diagnosis was associated with worse OS at univariate analysis (p = 0.017) (Figure 1(f)).

### 3.3. Fertility Outcomes
Among 61 patients attempting conception, 37 (61%) achieved 44 pregnancies (32 live births, 5 induced abortions, 6 spontaneous miscarriages, and 1 ectopic pregnancy). Ten patients had undergone IVF-ET, achieving 5 pregnancies. At the time of analysis, among these patients, 10 experienced invasive recurrence, and one died of progressive disease.

### 4. Discussion
To our knowledge, this is the most extensive series available that explores the oncofertility outcomes of women with SBOT-Ms and their related predictors. Compared to radical management, the conservative procedure was associated with decreased DFS rates but not associated with invasive-specific or overall survival. Advanced FIGO stage at diagnosis was the strongest predictor of invasive evolution of the

### Table 2: Prognostic factors for recurrence in women with SBOT-Ms (N = 200).

| Variables                  | Disease-free survival (DFS) | Univariate analysis | Multivariate analysis |
|----------------------------|-----------------------------|---------------------|----------------------|
|                            | N recur/total (%)           | 5-year DFS (%)      | p        | Hazard ratio (95% CI) | p      |
| Age (years)                |                             |                     |          |                      |        |
| > 35                       | 10/75 (13.3)                | 86                  | <.001    | 1                    | .018   |
| ≤ 35                       | 71/125 (56.8)               | 39                  |          | 2.4 (1.2-4.9)        |        |
| Nulliparous                |                             |                     |          |                      |        |
| Yes                        | 60/108 (55.6)               | 40                  |          |                      |        |
| No                         | 32/66 (48.5)                | 43                  |          |                      |        |
| Surgical approach          |                             |                     |          |                      |        |
| Laparotomy                 | 49/134 (36.6)               | 62                  | .066     |                      |        |
| Laparoscopy                | 32/66 (48.5)                | 43                  |          |                      |        |
| Staging surgery            |                             |                     |          |                      |        |
| Yes                        | 42/127 (33.1)               | 64                  | .015     | 1                    | .054   |
| No                         | 39/73 (53.4)                | 44                  |          |                      |        |
| Lymphadenectomy            |                             |                     |          |                      |        |
| Yes                        | 11/60 (18.3)                | 80                  | <.001    | 1                    | .281   |
| No                         | 70/140 (50.0)               | 45                  |          |                      |        |
| Surgical extent            |                             |                     |          |                      |        |
| Conservative               | 73/122 (59.8)               | 36                  |          | 5.8 (2.6-12.8)       |        |
| Unilateral                 | 21/63 (33.3)                | 62                  | .128     |                      |        |
| Ovarian involvement        |                             |                     |          |                      |        |
| Bilateral                  | 60/137 (43.8)               | 54                  |          |                      |        |
| FIGO stage                 |                             |                     |          |                      |        |
| I                          | 45/106 (42.5)               | 56                  | .904     |                      |        |
| II-IV                      | 36/93 (38.3)                | 57                  |          |                      |        |
| Stromal microinvasion      |                             |                     |          |                      |        |
| No                         | 71/164 (43.3)               | 54                  | .114     |                      |        |
| Yes                        | 10/36 (27.8)                | 65                  |          |                      |        |
| Type of implants (n = 94)  |                             |                     |          |                      |        |
| Noninvasive                | 25/68 (36.8)                | 58                  | .566     |                      |        |
| Invasive                   | 11/26 (42.3)                | 52                  |          |                      |        |
| Chemotherapy               |                             |                     |          |                      |        |
| Yes                        | 58/146 (39.7)               | 57                  | .887     |                      |        |
| Chemotherapy               | 23/54 (42.6)                | 54                  |          |                      |        |

1FIGO, International Federation of Gynecology and Obstetrics.
Patients at risk

- Radical group 78
- Conservative group 122

Follow-up period (months)

(a) Disease-free survival (DFS) according to treatment modalities

- Radical group 78
- Conservative group 122

Follow-up period (months)

(b) Invasive DFS according to treatment modalities

- Radical group 78
- Conservative group 122

Figure 1: Continued.
Patients at risk

Follow-up period (months)

Cumulative overall survival

(c) Overall survival according to treatment modalities

Non-invasive versus no implant: $p = 0.92$;
Invasive versus no implant: $p = 0.56$;
Invasive versus non-invasive: $p = 0.57$

Follow-up period (months)

Cumulative disease-free survival

(d) DFS according to stage groups and type of implants

Figure 1: Continued.
First, our findings support the feasibility of conservative therapy in young patients with SBOT-Ms and should be seriously discussed with these subjects. The 5-year DFS rate after conservative surgery in our series is 36.2%, which is significantly worse than that of the radical treatment group (88.7%, \(p < 0.001\)) (Figure 1(a)), as well as the probability reported for SBOT-Ms regardless of treatment modality, which varies from 61 to 86% [2, 17, 20]. However, 89% (\(n = 72/81\)) of our first recurrences were borderline lesions that could be cured readily by a second surgical procedure. Similar findings were also observed by Laurent et al. [20]; nearly 11 of 18 patients developed at least one recurrence at a median interval of 41 months, with only one patient experiencing lethal progression. Additionally, neither invasive DFS (Figure 1(b)) nor OS (Figure 1(c)) of patients undergoing conservative management was significantly different than that of women undergoing radical management (\(p = 0.452\) and 0.542, respectively). Thus, women with SBOT-Ms can be safely treated with FSS, but a high rate of recurrence is expected.

**Figure 1:** Survival curves in women with serous borderline ovarian tumor-micropapillary variants (SBOT-Ms).
Second, our work suggests an association between SBOT-Ms and lethal recurrence risk, especially for those with extraovarian implants. Nearly one-ninth of our patients (11.5%, \( n = 23/200 \)) experienced invasive relapse, including seven patients (3.5%) who eventually succumbed to their disease. This rate of invasive progress is comparable to that described in the literature review and national cohort studies for SBOT-Ms (11-21%) [5, 10, 18] and significantly higher than the widely reported rate for typical SBOTs (2-8%) [14, 15, 19, 27]. Additionally, in a systematic review by Vasconcelos et al. [5], 18.9% (\( n = 59/314 \)) and 12.4% (\( n = 78/632 \)) of patients with SBOT-Ms (regardless of stage) and advanced-stage disease (implants of any type, regardless of the presence of SBOT-Ms or not), respectively, progressed to invasive disease (\( p < 0.0005 \)). That is, patients with SBOT-Ms have a significantly higher rate of lethal recurrence than patients with advanced-stage SBOTs, and therefore, SBOT-Ms should be regarded as a high-risk factor for lethal recurrence, especially for those with peritoneal disease.

Several reasons may account for this. First, several high-risk features for lethal recurrence are highly prevalent in SBOT-M cases, namely, bilateral involvement, residual disease after surgery, advanced-stage disease, stromal microinvasion, and the presence of invasive implants, although the data are conflicting [5, 10–12, 14, 15, 18–20, 28, 29]. Second, sample bias might exist. Histologic review of LGSC slides revealed that 52% of LGSC cases had concurrent SBOT-Ms [30], implying that occult invasion might have been unsampled during the initial management of SBOT-Ms. Finally, molecular studies have demonstrated shared clonal and MAPK pathway mutations between SBOT-Ms and LGSCs [31], suggesting SBOT-M as a stepwise pattern from SBOT to invasive ovarian cancer. Thus, a thorough sampling with at least 2 sections/cm of maximum tumor diameter in both the primary SBOT-M tumors and extraovarian implants should be considered to rule out occult invasion [32, 33], and patients with SBOT-Ms would benefit from more aggressive staging surgery and intensive follow-up at an oncology center [23].

It is not surprising to identify younger age at diagnosis as an adverse predictor for recurrence. In our cohort, patients \( \leq 35 \) years were more likely to be treated with conservative surgery (25.3% versus 82.4%, \( p < 0.001 \)), to use the laparoscopic approach (40.0% versus 21.3%, \( p = 0.007 \)), and less likely to undergo adequate staging surgery (54.4% versus 78.7%, \( p = 0.001 \)), compared to those \( > 35 \) years. As shown in Table 2, all these factors were significantly associated with DFS in either univariate or multivariate analysis. Similar findings were also observed in the national cohort of the AGO ROBOT study [34], as well as in stage I SBOTs with conservative treatment [13]. However, both studies were conducted among the borderline/serous borderline

### Table 3: Prognostic factors for invasive recurrence in women with SBOT-Ms (N = 200).

| Variables                  | Invasive disease-free survival (DFS) | Univariate analysis | Multivariate analysis |
|----------------------------|-------------------------------------|---------------------|-----------------------|
|                            | N. lethal recur./total (%) | 5-year invasive DFS (%) | \( p \) value | Hazard ratio (95% CI) | \( p \) value |
| Age (years)                |                                   |                     |                     |
| \( \leq 35 \)              | 18/125 (14.4)                     | 87                  | .165                 |                     |                     |
| \( > 35 \)                | 5/75 (6.7)                       | 93                  |                      |                     |                     |
| Nulliparous                |                                   |                     |                     |
| Yes                       | 19/108 (17.6)                    | 86                  | 3.5 (1.2-10.4)       | .022                |                     |
| No                        | 4/92 (4.3)                      | 95                  | .009                 | 1                   | .022                |
| Surgical approach         |                                   |                     |                     |
| Laparotomy                | 17/134 (12.7)                   | 88                  | 5.74                 |                     |                     |
| Laparoscopy                | 6/66 (9.1)                     | 92                  |                      |                     |                     |
| Staging surgery           |                                   |                     |                     |
| Yes                       | 15/127 (11.8)                   | 90                  | .774                 |                     |                     |
| No                        | 8/73 (11.0)                    | 89                  |                      |                     |                     |
| Lymphadenectomy           |                                   |                     |                     |
| Yes                       | 7/60 (11.7)                     | 93                  | > .999               |                     |                     |
| No                        | 16/140 (11.4)                  | 89                  |                      |                     |                     |
| Surgical extent           |                                   |                     |                     |
| Radical                   | 7/78 (9.0)                     | 90                  | 0.452                |                     |                     |
| Conservative              | 16/122 (13.1)                  | 88                  |                      |                     |                     |
| Ovarian involvement       |                                   |                     |                     |
| Unilateral                | 2/63 (3.2)                     | 96                  | .015                 | 1                   | .112                |
| Bilateral                 | 21/137 (15.3)                  | 87                  |                      |                     |                     |
| FIGO stage                |                                   |                     |                     |
| I                         | 7/106 (6.6)                    | 95                  | .014                 | 1                   | .029                |
| II-IV                     | 16/94 (17.0)                  | 83                  | 1.6 (1.1-2.6)        |                     |                     |
| Stromal microinvasion      |                                   |                     |                     |
| Yes                       | 17/164 (10.4)                  | 92                  | .221                 |                     |                     |
| No                        | 6/36 (16.7)                    | 77                  |                      |                     |                     |
| Type of implants (\( n = 94 \)) |                   |                     |                     |
| Noninvasive               | 11/68 (16.2)                  | 83                  | .657                 |                     |                     |
| Invasive                  | 5/26 (19.2)                    | 77                  |                      |                     |                     |
| Chemotherapy              |                                   |                     |                     |
| Yes                       | 13/146 (8.9)                   | 93                  | .101                 |                     |                     |
| No                        | 10/54 (18.5)                   | 80                  |                      |                     |                     |

1FIGO, International Federation of Gynecology and Obstetrics.
population, without separating data on SBOT-Ms. Notably, for the first time, nulliparous was identified as an independent prognostic factor for invasive evolution (nulliparous versus parous, HR: 3.5, 95% CI: 1.2-10.4, p = 0.022). Nevertheless, in this nulliparous subgroup of women, there was a trend towards a higher rate of younger age at diagnosis (82.4% versus 39.1%, p < 0.001), bilateral tumors (76.9% versus 58.7%, p = 0.006), advanced stage at diagnosis (52.8% versus 40.2%, p = 0.076), and inadequate staging surgery (43.5% versus 28.3%, p = 0.025), compared to those parous women. As observed previously, nearly one-third of patients with “apparent stage I” SBOT-Ms were upstaged after adequate staging surgery [29, 32], and incomplete staging has an unfavorable impact on recurrence [4, 14]. That is, more patients might be upstaged if rigorous staging surgery had been performed in this nulliparous cohort, whereas advanced stage was independent associated with lethal relapse (HR: 1.6, 95% CI: 1.1-2.6, p = 0.029). In fact, stratification analysis of our data according to tumor stage revealed that nulliparous status was negatively associated with malignant transformation only in early-stage group (p = 0.016), but not in advanced-stage group (p = 0.23).

Last and foremost, our results indicate the stage-specific risk of malignant transformation for SBOT-Ms patients with recurrence. Compared with stage I disease, patients with extravarian implants doubled the risk of malignant transformation (HR: 1.6, 95% CI: 1.1-2.6, p = 0.029), especially for those experiencing recurrence. Among 36 patients with advanced-stage disease experiencing relapse, 44% (n = 16) were diagnosed with invasive carcinoma and had a subsequent impaired survival, which was significantly higher than those with stage I disease (n = 7/45, 16%). Similar findings were also reported by Uzan et al.; of 53 patients with stage II-III SBOT-Ms, 13 patients had relapsed, and six of them recurred as invasive disease [17], whereas of 18 patients with stage I, six had relapsed, and only one developed invasive disease [14]. Further supporting data were from the national Denmark cohort involving 80 SBOT-Ms (in whom 58 stage I); patients with advanced stage showed a trend toward increasing risk of developing serous carcinoma, although not statistical significance (HR = 2.6; 95% CI: 0.6–10.5; stage II-III versus I) [19]. Additionally, as reviewed by Vasconcelos et al., of 157 SBOT-M patients with lethal recurrence, only four occurred in the absence of peritoneal disease spread [5]. Several studies have postulated the type of implants and number of implants, and intratumoral heterogeneity might account for this apparent stage-specific invasive evolution [4, 10, 16, 29, 33]. However, the results from different studies are inconsistent, and comparable invasive DFS and OS were observed between invasive and noninvasive implants associated within our series (p = 0.66 and 87, respectively). Nevertheless, adequate staging surgery with careful exploration of all peritoneal surfaces and prolonged follow-up of these patients are justified, and further studies that explored early diagnosis of recurrence, particularly for invasive recurrences that are still localized, are urgently needed [35].

Of note, our study has several limitations. First, selection bias might exist due to the nature of all retrospective studies, although the study population was retrieved consecutively. Patients with “higher risk” features might be more inclined to select a more radical approach, and as observed in our cohort, more patients with advanced stage and invasive implants underwent radical surgery. However, there was no significant difference in either invasive recurrence or overall survival among the different treatment modalities, which reinforced the feasibility of fertility preservation in women with SBOT-Ms. Second, as referral centers, approximately one-third of the patients in the cohort were initially treated at an outside hospital and then referred to our institutions after recurrence; thus, referral bias is another weakness. A third limitation of the current study is that only two-thirds of the cases underwent complete staging during their initial surgery, which might underestimate the influence of extravarian implants on prognosis. As observed previously, nearly one-third of patients with “apparent stage I” SBOT-Ms were upstaged after accurate staging surgery [29, 32], and incomplete staging has an unfavorable impact on recurrence [4, 14]. Nonetheless, to our knowledge, the current series represents the largest published report to date that specifically addresses the oncofertility outcomes of women with SBOT-Ms.

In conclusion, our series suggests that conservative surgery is a safe and effective modality for the treatment of
young women with SBOT-Ms, with an acceptable oncological outcome and promising pregnancy result. The risk for lethal recurrence is not rare, especially for those with extra-ovarian implants experiencing relapse. Further studies that explore the potential malignant transformation mechanisms and postoperative surveillance modality are warranted.

**Data Availability**

Data is available on request by contacting jiashuangzheng@cicams.ac.cn.

**Conflicts of Interest**

All authors have nothing to declare.

**Authors’ Contributions**

Shuang-Zheng Jia contributed to the conceptualization, methodology, formal analysis, investigation, resources, and writing-original draft. Hong-Wen Yao contributed to the methodology, formal analysis, investigation, resources, and writing-original draft. Ning Li contributed to the conceptualization, formal analysis, and review and editing. Jun-Jun Yang contributed to the validation, resources, and review and editing. Yang Xiang contributed to the validation, resources, and review and editing. Ling-Ying Wu contributed to the conceptualization, validation, resources, supervision, and review and editing. Shan Zheng contributed to the resources and supervision. Jia Jun-Jun contributed to the validation, resources, supervision, and review and editing. Shuang-Zheng Jia contributed to the conceptualization, formal analysis, and review and editing.

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