

Long-term follow-up of patients with an isolated ovarian recurrence after conservative treatment of epithelial ovarian cancer: review of the results of an international multicenter study comprising 545 patients

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Objective: To determine the long-term outcomes of patients with an isolated ovarian recurrence after fertility sparing surgery (FSS) for epithelial ovarian cancer (EOC) and to evaluate the recurrence rates (and location) according to the new 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system.

Design: Retrospective multicenter study.

Setting: Teams having reported recurrence after FSS for EOC.

Patient(s): Four series comprising 545 patients undergoing FSS and 63 (12%) recurrences.

Intervention(s): FSS (salpingo-oophorectomy for a majority of cases) for EOC.

Main Outcomes Measure(s): Recurrences rates and characteristics of recurrent disease.

Result(s): Among 63 recurrent patients, 24 (38%) recurrences were isolated on the spared ovary, and 39 (62%) arose at an extraovarian site. Among the patients with an isolated ovarian recurrence, three patients died after a median follow-up period of 186 months (range: 28–294 months). Among the patients with recurrent extraovarian disease, 24 died and 7 were alive with persistent disease after a median follow-up period of 34 months (range: 3–231 months). The overall rate of isolated ovarian and extrapelvic recurrences was higher for grade 3 tumors (compared with grades 1/2).

Conclusion(s): The long-term survival of patients with an isolated ovarian recurrence after FSS for EOC remains favorable. The prognosis of patients with an extraovarian recurrence is poor compared with those who have an isolated recurrent ovarian tumor. Grade 3 tumors (compared to grades 1/2) give rise to a higher rate of extraovarian recurrences. (Fertil Steril® 2015;104:1319–24. ©2015 by American Society for Reproductive Medicine.)

Key Words: Conservative surgery, epithelial ovarian tumor, extraovarian recurrence, prognosis, recurrence

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Conservative treatment of epithelial ovarian cancer (EOC) is based on unilateral salpingo-oophorectomy and complete surgical staging. This is an option available to young women who present with an early-stage invasive tumor with a low

risk of recurrence (1–3). The outcomes for patients seem to be similar to those after conventional treatment of patients with stage IA (grades 1 and 2) and stage IC (grade 1) disease (1–3). In the case of patients with stages IA and IC grade 3 disease and stage IC grade 2 tumors, the results of conservative management continue to fuel debate (1). To have a complete overview of the different issues likely to exert an impact on oncologic results in this context, an analysis of the prognosis after a first recurrence after conservative treatment of EOC is crucial. A single study on this topic was published nearly a decade ago, which featured a short follow-up period (4). The long-term outcomes of such patients are unknown.

The outcome of patients with an extraovarian recurrence as the first event is poor (akin to that of patients with ovarian cancer and peritoneal spread) (4). But the long-term outcomes of patients with an isolated recurrence on the spared ovary as a first event remain undetermined. With the 2014 International Federation of Gynecology and Obstetrics (FIGO) classification modifications (particularly concerning early stage disease with the creation of the “IC” group), oncologic results of the different series published on this topic should be reevaluated in the light of the new FIGO system to identify the potential oncologic safety limits of conservative treatment within the stage IC group (5). Our study [1] determined the long-term outcomes of patients with an isolated recurrence on the spared ovary and [2] evaluated the recurrence rates (between ovarian and extraovarian sites) after conservative treatment according to the 2014 FIGO staging system (5).

MATERIALS AND METHODS

We reviewed the data of patients treated conservatively for an EOC and involving at least 10 cases as reported in the literature (6–24). We selected published series (excluding those published exclusively as abstracts with no full publication) that reported at least one isolated ovarian recurrence. In cases of repeated publication by the same team, only the most recent update (or the series by the same team reporting on the largest number of recurrences) was retained for further analysis. The studies derived from five different countries on three continents; the senior authors of these series were contacted to update the data on patients with recurrent disease (10, 14, 17, 22, 23). Among the five teams contacted who had published at least one article involving our criteria, four had updated the outcomes of their patients with recurrent disease (10, 17, 22, 23). Institutional review board (University Paris Sud) approval was obtained.

We analyzed the patient characteristics for each study. For stage IC disease, after reviewing the descriptions of the patients we reclassified them as having stage IC1 (peroperative rupture), IC2 (preoperative rupture), or IC3 (positive cytology or positive ascites) by the 2014 FIGO staging system (5). If the data were insufficient to classify the patients with IC disease, we classified them as having IC “unknown” disease (Table 1). Similarly, for some studies it was not possible to correlate the tumor grade and the FIGO classification; in these cases, the patients were classified as stage IA or IC with an “unknown grade” (Table 1).

The characteristics of the patients with recurrent disease were reanalyzed with a focus on our primary and secondary objectives. Our primary aim was to evaluate the long-term survival of patients with an isolated first recurrence on the spared ovary. Our two secondary objectives were [1] to classify the recurrent disease location (isolated ovarian recurrences on the remaining ovary or extraovarian recurrences with or without combined ovarian disease) according to the 2014 FIGO staging classification (with a correlation between the initial characteristics of the tumor and the location of these recurrences); and [2] to evaluate the survival of patients with an extraovarian recurrence.

The analyses were performed using the chi-square or Fisher exact tests for qualitative data. All analyses were performed with OpenStat for Windows (<http://statpages.info/miller/OpenStatMain.htm>). $P < .05$ was considered statistically significant for all analyses.

RESULTS

The four series analyzed comprised 545 patients. The characteristics of these patients are detailed in Table 1. Half of the patients ($n = 280$; 51%) had a mucinous tumor. Two-thirds of the patients ($n = 357$; 65%) had a grade 1 lesion, and 20% ($n = 107$) had grade 2 disease. The majority of patients had stage IA disease ($n = 316$; 58%), and 41% ($n = 222$) had stage IC. Logically, in this context a minority of patients had stage IB disease (see Table 1).

Among the 63 (11.6%) patients who developed a recurrence, in 24 (38%) it was isolated on the spared ovary, and in 39 (62%) it comprised an extraovarian site. The median time to the recurrence was 21 months (range: 2–172 months). Twenty-seven (6%) patients died of their recurrence. Thirty-seven patients had received adjuvant treatment during the initial treatment. The characteristics of the patients with recurrent disease are shown in Table 1.

The recurrence rate was higher for serous neoplasms at 20.6% compared with mucinous at 6.8% ($P < .001$) (see Table 1). This rate approached the level of statistical significance for stage IC (14%) compared with IA at 9.2% ($P = .08$). The recurrence rate was statistically significantly higher for grade 3 tumors (23.5%) compared with grades 1 (9%) and 2 (11.2%) ($P < .001$), and for stage IC grade 3 disease (27%) compared with IC grades 1 (10.7%) and 2 (10.2%) ($P = .01$). The recurrence rate was close to statistical significance for stage IC3 (18.6%) compared with IC1 (9.2%) ($P = .09$).

Among the 24 patients with an isolated ovarian recurrence, the median age at initial management was 26 years (range: 16–37 years). The median time to recurrence was 43 months (range: 2–172 months). The details of the adnexal surgery were available for 19 patients. Thirteen had undergone a salpingo-oophorectomy, and six had undergone a simple cystectomy. Eleven had undergone staging procedures. The histologic subtypes, tumor grade, and FIGO staging system are detailed in Table 2. None of these characteristics appeared to impact the outcomes of patients with an isolated ovarian recurrence. After a median follow-up of 186 months (range: 28–294 months), three patients had died, and one was alive with persistent disease. The patient who was alive with

TABLE 1

Characteristics of patients with a recurrence.

Characteristic	N	Patients with a recurrence, n (%)	P value	Recurrence location		P value
				Ovarian, n (%)	Extraovarian, n (%)	
Total	545	63 (11.6)		24 (38)	39 (62)	
Histologic subtypes						
Serous	97	20 (20.6)	< .001 ^a	10 (50)	10 (50)	.4 ^a
Mucinous	280	19 (6.8)		7 (37)	12 (63)	
Endometrioid	103	13 (12.6)		5 (39)	8 (62)	
Clear cell	59	9 (15.3)		1 (11)	8 (89)	
Mixed	4	2 (50)		1 (50)	1 (50)	
Unknown	2	–	–	–		
Grade						
Grade 1	357	32 (9)	< .001 ^b	19 (59)	13 (41)	.001 ^b
Grade 2	107	12 (11.2)		4 (33)	8 (67)	
Grade 3	81	19 (23.5)		1 (5)	18 (95)	
FIGO stage						
IA	316	29 (9.2)	.08 ^c	11 (38)	18 (62)	.8 ^c
IA grade 1	192	13 (6.8)		8 (62)	5 (38)	
IA grade 2	58	6 (10.3)		3 (50)	3 (50)	
IA grade 3	36	8 (22.2)		–	8 (100)	
IA grade unknown	30	2		–	2	
IB	3	1 (33.3)	1 (100)	–		
IC	222	31 (14)	.09 ^e	11 (35)	20 (65)	.4 ^e
IC1	129	12 (9.2)		5 (44)	7 (56)	
IC2	46	7 (15.2)		3 (43)	4 (57)	
IC3	43	8 (18.6)		2 (25)	6 (75)	
IC unknown	4	4		1	3	
IC grade 1	121	13 (10.7%)	.01 ^f	8 (62)	5 (38)	.04 ^f
IC grade 2	39	4 (10.2)		1 (25)	3 (75)	
IC grade 3	33	9 (27%)		1 (11)	8 (88)	
IC grade unknown	29	5		1	4	
II	4	2 (50)		1 (50)	1 (50)	

Note: FIGO = International Federation of Gynecology and Obstetrics.

^a Serous versus mucinous.

^b Grade 3 versus grade 1 + 2.

^c IC versus IA.

^d IA grade 3 versus grade 1 + 2.

^e IC3 versus IC1.

^f IC grade 3 versus IC grade 1 + 2.

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persistent disease was lost to follow-up observation 28 months after the initial treatment.

The first patient who died was a 16-year-old adolescent who had undergone a unilateral salpingo-oophorectomy for a stage IA grade 2 mucinous tumor. She received complete peritoneal and nodal staging surgery without adjuvant chemotherapy. Her recurrence was 2 months later on the contralateral ovary with positive ascites. Six months later, the disease had spread to the nodes; she died 54 months after the initial treatment.

The second deceased patient had undergone a similar initial treatment at 18 years of age for a stage IA grade 1 mucinous tumor. Her recurrence was on the contralateral ovary 9 months later, with vulvar, bone, and brain metastases 23 months after the ovarian recurrence. She died of the disease 40 months after the initial treatment.

The third patient, a 28-year-old woman, was treated for stage IB grade 1 disease. She refused radical treatment and received adjuvant chemotherapy. She developed an isolated ovarian recurrence 34 months later, and she died of a peritoneal recurrence 196 months after the initial treatment.

Among the 39 patients with an extraovarian recurrence, the median age at initial treatment was 30 years (range: 14–40 years). The median time to recurrence was 14 months (range: 1–73 months). The details concerning the adnexal surgery were available for 26 patients. Twenty-one women had a salpingo-oophorectomy, and five had a simple cystectomy. Twelve patients had undergone staging procedures. After a median follow-up of 34 months (range: 3–231 months), 24 had died, and 7 were alive with persistent disease. The histologic subtypes, tumor grade, FIGO staging system, and details on outcomes according to these criteria are shown in Table 3.

Thus, the lethality of an extraovarian recurrence is higher compared with an isolated ovarian recurrence: 24 (62%) of 39 versus 3 (13%) of 24 ($P < .001$). In the subgroup of patients with extraovarian recurrence, the rate of patients with no evidence of disease is higher in those with stage IA compared with IC disease: 6 (33%) of 18 versus 2 (10%) of 20 ($P = .08$). This rate was not statistically different when comparing serous with mucinous tumors: 3 (30%) of 10 versus 1 (8%) of 12 ($P = .1$). Others factors had no impact on the outcomes with extraovarian recurrences (see Table 3).

TABLE 2

Characteristics and outcomes of 24 patients with an ovarian recurrence.

Characteristic/outcome	No. of patients	Current status, n (%)
Total	24	3 DOD (13) 1 AWD (4) 20 NED (83)
Histologic subtypes		
Serous	10	1 DOD (10) 1 AWD (10) 8 NED (80)
Mucinous	7	2 DOD (29) 5 NED (71)
Endometrioid	5	5 NED (100)
Clear cell	1	1 NED (100)
Mixed	1	1 NED (100)
Tumor grade		
Grade 1	19	2 DOD (11) 1 AWD (5) 16 NED (84)
Grade 2	4	1 DOD (25) 3 NED (75)
Grade 3	1	1 NED (100)
FIGO stage		
IA	11	2 DOD (18) 9 NED (82)
IA grade 1	8	1 DOD (12) 7 NED (88)
IA grade 2	3	1 DOD (33) 2 NED (67)
IB grade 1	1	1 DOD (100)
IC	11	1 AWD (9) 10 NED (91)
IC1	5	5 NED (100)
IC2	3	1 AWD (33) 2 NED (67)
IC3	2	2 NED (100)
IC unknown	1	1 NED (100)
IC grade 1	9	1 AWD (11) 8 NED (89)
IC grade 2	1	1 NED (100)
IC grade 3	1	1 NED (100)
II	1	1 NED (100)

Note: AWD = alive with persistent disease; DOD = died of disease; FIGO = International Federation of Gynecology and Obstetrics; NED = no evidence of disease.

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In terms of the location of the recurrent disease, there was no statistically significant difference in the recurrence rates between stage IC grade 1 and IC grade 2; however, the rate of extraovarian recurrences was higher for stage IC grade 2 although it did not reach the level of the significance (75% versus 38%; $P=.2$). The rate of extraovarian recurrences was higher for stage IA grade 3 disease (100%) as compared with IA grade 1 (38%) and IA grade 2 (50%) ($P<.001$) and for IC grade 3 disease (88%) compared with IC grade 1 (38%) and IC grade 2 (75%) ($P=.04$).

DISCUSSION

We have fully evaluated the published results of conservative treatment of EOC, a type of management that is considered oncologically safe for early stage disease with favorable prognostic factors (1–3). However, for patients with stage I and intermediate (or clearly the poorest) prognostic factors

TABLE 3

Characteristics and outcomes of 39 patients with extraovarian recurrences.

Characteristic/outcome	No. of patients	Current status, n (%)
Total	39	24 DOD (62) 7 AWD (18) 8 NED (20)
Histologic subtypes		
Serous	10	7 DOD (70) 3 NED (30)
Mucinous	12	8 DOD (67) 3 AWD (25) 1 NED (8)
Endometrioid	8	5 DOD (63) 3 NED (37)
Clear cell	8	3 DOD (38) 4 AWD (50) 1 NED (12)
Mixed	1	1 DOD (100)
Tumor grade		
Grade 1	13	8 DOD (62) 3 AWD (23) 2 NED (15)
Grade 2	8	6 DOD (75) 2 NED (25)
Grade 3	18	10 DOD (56) 4 AWD (22) 4 NED (22)
FIGO stage		
IA	18	10 DOD (56) 2 AWD (11) 6 NED (33)
IA grade 1	5	3 DOD (60) 1 AWD (20) 1 NED (20)
IA grade 2	3	1 DOD (33) 2 NED (67)
IA grade 3	8	4 DOD (50) 1 AWD (12) 3 NED (38)
Unknown	2	2 DOD
IC	20	13 DOD (65) 5 AWD (25) 2 NED (10)
IC1	7	4 DOD (57) 3 AWD (43)
IC2	4	3 DOD (75) 1 NED (25)
IC3	6	5 DOD (83) 1 AWD (17)
IC unknown	3	1 DOD (33) 1 AWD (33) 1 NED (33)
IC grade 1	5	2 DOD (40) 2 AWD (40) 1 NED (20)
IC grade 2	3	3 DOD (100)
IC grade 3	8	4 DOD (50) 3 AWD (37.5) 1 NED (12.5)
IC grade unknown	4	4 DOD (100)
II	1	1 DOD (100)

Note: AWD = alive with persistent disease; DOD = died of disease; FIGO = International Federation of Gynecology and Obstetrics; NED = no evidence of disease.

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(stage IC, grade 3 disease), the results of this strategy continue to fuel debate. Our aim was not to evaluate the overall recurrence rate after such treatment (as this has been

known for at least 15 years) or the prognostic factors for recurrences in this context (as they have also been well identified) (1–3), but to focus on specific questions about the characteristics and outcomes of patients with recurrent disease in this context. Our current series, comprising the largest number of patients treated conservatively for EOC, and logically the largest number of patients with recurrences reported after such management, could help answer some of the remaining uncertainties.

Information on the specific outcomes of patients with recurrences is crucial in this context. Regardless of the oncologic indications for conservative management, the patient's survival is the foremost consideration. The single study 8 years ago by Marpeau et al. (4) to address this question contained two important messages. [1] The curability of patients with an isolated ovarian recurrence is higher than that of patients with an extraovarian recurrence (4). This is not surprising because the prognosis of patients with a recurrence in the form of distant metastasis would necessarily be worse than that of patients with a single site of recurrence. Unfortunately, in that study the number of patients with an isolated recurrence was low: 8 patients/34% of recurrences (4). [2] The risk of extraovarian recurrence is higher in the patients with “debatable” indications for conservative management of EOC (stage IC, grade 3 disease) (4). By running the risk of a potential recurrence (because the patient's status is a borderline indication), we increase the risk of the patient developing an incurable lesion (4). On the other hand, we could also hypothesize that such extraovarian recurrences are related to the natural history of the disease and to the presence of “intermediate” or the “poorest” prognostic factors rather than to a preserved ovary in itself.

The conclusions of Marpeau et al. (4) were limited by the small number of recurrences they studied (23 patients) and the short duration of their follow-up period. Hence, we decided to improve the evaluation's interpretability by increasing the number of cases and prolonging the follow-up period. We were mainly concerned with outcomes for the patients who have an isolated ovarian recurrence because, as previously suggested by Marpeau et al. (4), those with extraovarian disease have the lowest survival rate. The prognosis in the latter cases is very close to that of patients with stage III EOC (except for the particular case of patients with an isolated nodal recurrence).

The results of our current review demonstrate that the long-term survival of patients with an isolated ovarian recurrence remains relatively favorable. Consequently, long-term outcomes will not be compromised if such an event occurs. Isolated ovarian recurrences are more frequently observed in patients with favorable prognostic factors and conventional indications for conservative treatment, thus validating the safety of such management in this subgroup (4). However, we also confirm that only a minority of patients will develop an isolated recurrence on the spared ovary.

Our study confirms that the rate of extraovarian recurrences is higher in patients with intermediate prognostic factors (grade 3 for stage IA/IC and grade 2 for stage IC). In the case of grade 3 tumors, 95% of recurrences were extraovarian, and only 22% of them were rendered disease free (see Table 3).

Our series also confirms the higher lethality when such events occur (compared with isolated ovarian recurrences). These points are important considerations when counseling patients about their management options.

The other key message concerns the specific subgroup of patients with stage IC disease. Previously, different clinical situations had been combined within this subgroup, which explains why the series reported in this context had different outcomes for patients treated conservatively for stage IC disease. Thus, the new 2014 FIGO staging system is genuinely helpful in differentiating the potential prognoses of stages IC1, IC2, and IC3 disease (5). Our review is the first to specifically evaluate oncologic results (and the locations of recurrences) according to the new FIGO classification (1).

Our review confirms that the recurrence rate is acceptable (and seems to be similar to that observed with conventional treatment) for stage IC1 disease with preoperative rupture (half of these recurrences were isolated on the remaining ovary) (Table 1). But in the case of stages IC2 and IC3, the recurrence rates are higher, from 9.2% in IC1 to 18.6% in IC3. Furthermore, three-quarters of the recurrences were extraovarian after a stage IC3 primary tumor (75%). In like manner, if we take into account the tumor grade, patients with stage IC grade 2 disease have the same risk of recurrence as those with stage IC grade 1 disease but with a trend toward a higher risk of extraovarian recurrence (75% versus 38%). It is unclear whether such extraovarian (and thus less curable) recurrences are related to the natural history of the disease (in grade 3 and/or stage IC grade 2 and/or stage IC3 disease) or to the use of fertility-sparing surgery itself.

The number of patients treated conservatively for a more advanced stage of the disease (>I or bilateral tumors/stage IB) is low, but the recurrence rate is high, suggesting that conservative surgery should not be proposed to patients whose disease exceeds stage >I (25).

In conclusion, our results confirm that the long-term survival of patients with an isolated ovarian recurrence after fertility-sparing surgery in EOC is better than that of patients with other sites of recurrence. Such recurrences were observed in patients with favorable prognostic factors (in terms of the histologic subtype, stage, and tumor grade) who were thus considered to have conventional indications for conservative treatment. The prognosis of patients with an extraovarian recurrence is very poor. The rate of such recurrences is higher in cases of stage IC3 (compared with IC1/IC2) and grade 3 tumors (compared with grades 1/2), suggesting that such features could be perhaps considered the limits of safety for conservative treatment. It is unclear whether such extraovarian (and thus less curable) recurrences are related to the natural history of the disease (in grade 3 and/or stage IC grade 2 and/or stage IC3 disease) or to the use of fertility-sparing surgery in itself. Patients with less favorable prognostic factors (grade 3 or stage IC3 disease) should be informed that a radical treatment might not necessarily improve their oncologic outcome. The uncertainties are important information to impart to patients in these different clinical situations, namely, a tumor with intermediate (stage IC grade 2) or clearly less favorable prognostic factors (grade 3 or stage IC3 disease).

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