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Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series

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Background: To assess the long-term oncological outcome and the fertility of young women with early-stage epithelial ovarian cancer (ES/EOC) treated with fertility-sparing surgery (FSS).

Patients and methods: All patients treated with FSS for ES/EOC in two Italian centers were considered for this analysis. Univariate and multivariate analyses were used to test demographic characteristics and clinical features for the association with overall survival (OS), recurrence-free survival (RFS) and fertility.

Results: From 1982 to 2010, 240 patients with malignant ES/EOC were treated with FSS in two tertiary centers in Italy. At a median follow-up of 9 years, 27 patients had relapsed (11%) and 11 (5%) had died of progressive disease. Multivariate analysis found only grade 3 negatively affected the prognosis of patients [hazard ratio (HR) for recurrence: 4.2, 95% confidence interval (CI): 1.5–11.7, $P = 0.0067$; HR for death: 7.6, 95% CI: 2.0–29.3, $P = 0.0032$]. Grade 3 was also significantly associated with extra-ovarian relapse ($P = 0.006$). Of the 105 patients (45%) who tried to become pregnant, 84 (80%) were successful.

Conclusions: Conservative treatment can be proposed to all young patients when tumor is limited to the ovaries, as ovarian recurrences can always be managed successfully. Patients with G3 tumors are more likely to have distant recurrences and should be closely monitored.

Key words: fertility-sparing surgery, obstetrical outcome, ovarian cancer, survival

introduction

Epithelial ovarian cancer (EOC) is a postmenopausal disease, as it is more frequent in the fifth and sixth decades. Moreover, the majority of EOC patients are diagnosed when there is already abdominal spread of the disease. However, ~25% are limited to the ovaries at diagnosis, and 14% of invasive ovarian cancers are in women <40 years old [1].

Fertility-sparing surgery (FSS) for women of childbearing age with early-stage malignant epithelial ovarian cancer (ES/EOC) has been intensely debated in the last two decades. Preservation of the reproductive tract in young women who want children, especially if nulliparas, is a widely understood need, in light of the excellent prognosis of women with ES/EOC. Historically, hysterectomy and bilateral salpingo-oophorectomy have been considered part of the initial surgical approach to ovarian cancer, regardless of the stage of the disease. ESMO guidelines still recommend these procedures even for stage I to II ovarian cancer patients, though uterus preservation and unilateral salpingo-oophorectomy are admitted in selected cases. Preservation of the adnexa and uterus is currently recommended in patients with non-epithelial tumors and epithelial borderline ovarian cancer, but is still considered suboptimal for women with invasive EOC, and there is general concern about the greater risk of relapse for patients who preserve the uterus and ovaries [2, 3].

There are only a few published series about conservative management of ES/EOC [4–13], and none are conclusive, as no randomized clinical trial has yet been done and, for ethical and practical reasons, none is likely in the future. Therefore, it

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Table 1. Published reports on conservative management of epithelial ovarian cancer and authors' recommendations

Author	Year	Number of patients	Stage			Grade			Relapses, *n* (%)	Deaths, *n* (%)	Fertility-sparing surgery recommendation
			IA	IB	IC	1	2	3			
Zanetta et al. [4]	1997	56	32	2	22	35	14	7	5 (9)	3 (5)	All stages I and grades
Schilder et al. [5]	2002	52	42	0	10	38	9	5	5 (10)	2 (4)	All stages I and grades
Morice et al. [6]	2005	34	30	0	3	15	15	4	10 (29)	4 (12)	Stage IA, G1
Borgfeldt et al. [7]	2007	11	10	0	1	9	1	1	1 (9)	1 (9)	Stage IA, not conclusive on grade
Park et al. [8]	2008	62	36	2	21	48	5	9	11 (18)	6 (10)	Stage IA to IC, G1 to G2
Anchezar et al. [9]	2009	16	11	0	5	14	1	1	2 (13)	1 (6)	All stages I and grades
Schlaerth et al. [10]	2009	20	11	0	9	15	5	1	3 (15)	3 (15)	All stages I and grades
Kwon et al. [11]	2009	21	17	0	4	16	3	2	1 (5)	0 (0)	Not conclusive on stage and grade
Satoh et al. [12]	2010	211	126	0	85	160	15	36[a]	18 (9)	5 (2)	All stages I, G1 to G2
Kajiyama et al. [13]	2010	60	30	1	29	41	7	12[b]	8 (13)	7 (12)	All stages I, G1 to G2
Our experience		240	130	2	105	141	70	29	27 (11.0)	11 (5)	All Stages I and grades
Total		783	475	7	294	532	145	107	91 (12)	43 (6)	

[a]Six G3 tumors and 30 clear-cell tumors.
[b]Two G3 tumors and 10 clear-cell tumors.

is not clear what 'selected cases' means, and there is no agreement about this point among groups. Table 1 illustrates this lack of consensus, summarizing the studies that have been published on fertility preservation in ES/EOC patients so far. Each author proposes different criteria for selecting candidates for FSS, mainly based on the International Federation of Gynecology and Obstetrics (FIGO) stage and grade of nuclear differentiation. Some authors, such as Morice et al. [6], use restrictive criteria to admit patients to conservative treatment, while others, such as Shilder et al. [5], consider all stage I ovarian cancer patients eligible for this treatment. This article presents the oncological and obstetrical outcome of a series of conservatively treated ES/EOC patients, to contribute to unraveling the complexity of this scenario.

patients and methods

Women of childbearing age with a strong desire to retain fertility treated with conservative surgery for EOC confined to the ovaries were included in this retrospective analysis. Patients were treated at San Gerardo Hospital (Monza) and at the European Institute of Oncology (IEO, Milan) or referred to one of these centers after FSS elsewhere. The two centers share the same approach for this group of patients. Patients with borderline EOC, ovarian germ cell tumors or stromal tumors were excluded.

The protocol of this analysis has been notified to the Local Ethics Committee.

Patients were staged according to the FIGO (1987) criteria [14], using macroscopic findings and histological analysis of specimens obtained during initial and restaging surgery. Pathology slides were reviewed by one pathologist from each institution and a centralized pathological review has not been carried out. Histological cell type and tumor differentiation were assessed according to the World Health Organization criteria.

The treatment plan for each patient was based on the adequacy of staging at first surgery. Surgery was considered adequate if cystectomy or unilateral adnexectomy was done, with peritoneal washing, omentectomy, careful inspection of the abdominal cavity with at least eight peritoneal biopsies (pelvic sidewalls, paracolic gutters, both diaphragms, pouch of Douglas, prevescical space), endometrial biopsy and evaluation of pelvic and para-aortic lymph nodes (meant as inspection and palpation with removal of any suspicious node, systematic lymphadenectomy or node sampling with at least 10 nodes).

Patients with adequate staging surgery received six cycles of single-agent cisplatin or carboplatin if they had a grade 3 tumor or an FIGO stage IC. Patients with inadequate initial staging surgery received six cycles of mono-chemotherapy with carboplatin if considered at high risk (FIGO stage IC to II or G2 to G3) and at the end of the cycles underwent second-look surgery or were closely monitored; they were considered eligible for follow-up surgery only according to clinical and histopathological risk factors if they were considered at low risk (FIGO stage IA to B, G1). Since our centers participated in both ICON1 [15] and ACTION [16] trials, some patients received chemotherapy according to randomization in the two studies.

OS was defined as the time from surgery to the date of death from any cause or the date of the last follow-up. Patients known to be alive at the time of analysis were censored at their last available contact date. RFS was defined as the time from surgery to the first appearance of relapse or the date of death for any cause; patients known to be alive and free of relapse at the time of analysis were censored at their last available follow-up.

Survival curves were estimated with the Kaplan–Meier method. Cox proportional hazards models were used for univariate and multivariate analyses to test demographic characteristics and clinical features for their associations with RFS and OS. The results are expressed as hazard ratios (HRs) and their 95% confidence intervals (95% CIs). Univariate and multivariate logistic regression models were used to assess the effects of clinical features on obstetrical outcome. In order to adjust for the effect of chemotherapic treatment, this variable was included in the multivariate model. The results are expressed as odds ratios (ORs) and 95% CIs. Fisher's exact test was used to compare proportions. Statistical significance was set at $P < 0.05$ for a bilateral test. Analysis was carried out using the SAS (Statistical Analysis System, SAS Institute, Inc., Cary, NC, Version 9.1) software.

results

From 1982 to 2010, a total of 240 patients with EOC apparently confined to the ovaries were treated with a fertility-sparing approach: 196 (82%) at San Gerardo Hospital, Monza, and 44 (18%) at the IEO, Milan.

Table 2 summarizes the clinical and tumor characteristics of the sample. Median age was 32 years, ranging from 15 to 38, and 71% patients were nullipara. Almost all women had a stage I ovarian cancer, with similar distribution of stages IA and IC. Tumor differentiation was well, moderate and poor in, respectively, 59%, 29% and 12% of patients. The most frequent histotype was mucinous (41%), followed by serous (26%) and endometrioid (25%).

Table 2. Clinical and tumor characteristics of patients treated with conservative surgery

	n (%)
Median age (range)	32 (15–38)
Stage	
IA	130 (54)
G1	84
G2	31
G3	15
IB	2 (1)
IC[a]	105 (44)
G1	54
G2	37
G3	14
IIA	1 (0.4)
IIB	2 (1)
Grade	
1	141 (59)
2	70 (29)
3	29 (12)
Hystotype	
Serous	62 (26)
Mucinous	99 (41)
Endometrioid	60 (25)
Clear cell	17 (7)
Unknown	2 (1)
Nulliparity	170 (71)
Adequacy of first surgery	
Yes	51 (21)
No	189 (79)
Restaging	61 (32)
Follow-up	91 (48)
No surgery	37 (20)
Type of surgery	
Laparotomy	191 (80)
Laparoscopy	49 (20)
Surgical procedures	
Cystectomy	62 (26)
Unilateral	54 (87)
Bilateral	8 (13)
Salpingo-oophorectomy	178 (74)
Omentectomy	74 (31)
Peritoneal biopsies	74 (31)
Lymph node evaluation	36 (15)
Lymphadenectomy	18 (50)
Sampling	18 (50)
Endometrial biopsy	61 (25)
Controlateral ovary biopsy	120 (50)
Chemotherapy	106 (44)
Monochemotherapy	88 (83)
Polichemotherapy	19 (17)
Median number of cycles received (range)	6 (1–6)
Completion surgery	18 (8)

[a]Reason for IC stage: positive cytology, 22 patients; surface involvement, 25 patients; rupture, 58 patients.

Figure 1 shows Kaplan–Meier curves for recurrence-free and overall survival. At a median follow up of 9 years (range 12–319 months), 27 patients relapsed. Details of relapsing patients are given in Table 3. Relapses were localized on the ovary in 13 cases, while 14 patients had distant (peritoneal) recurrence. Eleven died of progressive disease; one was receiving chemotherapy for persistent disease at the date of the analysis and 15 were alive without tumor. All 11 dead patients had an extra-ovarian recurrence. Four patients died of other causes.

Supplementary Figure S1, available at *Annals of Oncology* online, shows the outcomes according to the treatment received. Out of the 112 patients optimally staged at first surgery or immediately restaged, 51 (45.5%) received chemotherapy, 11 (10%) relapsed and 5 (4.5%) died. Treatment of the 128 patients who did not have a correct staging surgery was based on clinical and histopathological risk factors. In detail, 55 considered at high risk received chemotherapy, followed by second-look surgery in 80%; 11 (20%) out of these 55 had a relapse and 5 (9%) died; 73 low-risk patients did not receive chemotherapy and were followed closely; 5 (7%) relapsed and only one died.

Overall, 106 patients received a median number of 6 cycles of platinum-based chemotherapy (range 1–6).

Cystectomy was carried out in 62 patients (Table 2). Relapses occurred in 11 of these 62 patients (17%) and in 17 of 178 (9%) patients who underwent oophorectomy (Fisher's exact test *P*-value 0.09). However, the higher relapse rate in the group of patients treated with cystectomy did not lead to a higher death rate. In fact, these patients had more frequently an ovarian relapse (6 of 11 versus 7 of 16) and were successfully treated with a second surgery. On the other hand, 9 of 16 patients treated with oophorectomy had an extraovarian relapse, and only one of them is alive without disease (7 died, 1 is currently receiving chemotherapy). Overall, the mortality rate in the two groups is similar (4 of 62, 6% for

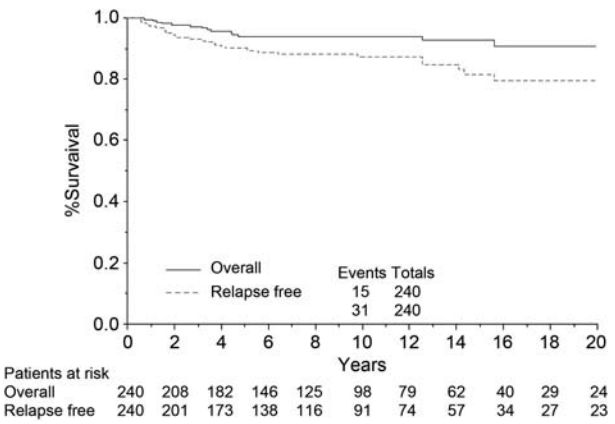

Figure 1. Kaplan–Meyer curves for recurrence-free survival and overall survival.

Table 3. Clinical details of relapsing patients

Patient ID	Stage	Grade	Hystotype	Staging[a]	Chemo[b]	2 Surgery[c]	PFS	Relapse site	Ovarian status at relapse	Management	Relapse surgical treatment[a]	Relapse chemo treatment	Past treatment parity	Status[d]	Overall survival
1	IC[e]	1	Endometroid	E, end	Yes	II Look	14	Homolateral ovary		Conservative	A, Bps	Yes	Sterility	NED	28
23	IIB	1	Serous	A, O, Bps, Lgh	Yes	II Look	151	Controlateral ovary		Conservative	A, end, Bps	No	1	NED	189
50	IA	2	Mucinous	E, O, Bps, end	Yes	II Look	20	Pelvis-abdomen	Negative	Conservative	Bps	Yes		DOD	41
57	IC[f]	1	Serous	A, O, Bps, Lgh	No	–	118	Controlateral ovary		Radical	A, H	No		NED	194
59	IA	1	Endometrioid	A	No	Restaging	172	Controlateral ovary		Radical	A, H, O, Lgh	No	Sterility	NED	218
60	IA	1	Mucinous	E	Yes	Restaging	19	Controlateral ovary		Conservative	A	No		NED	125
69	IC[g]	2	Mucinous	A, O, Bps, Lgh	Yes	–	25	Pelvis-abdomen	Positive	Radical	A, H, T	Yes		DOD	38
76	IA	1	Serous	A, O, Bps,Lgh	No	II Look	77	Controlateral ovary		Radical	A, H, O	No	1	NED	133
84	IA	3	Endometrioid	A	Yes	–	40	Pelvis-Abdomen	–	–	–	Yes		DOD	53
108	IC[eg]	2	Serous	A	No	Restaging	10	Pelvis-abdomen	Positive	Radical	A, H	Yes		DOD	23
117	IC[e]	1	Serous	A	No	II Look	44	Controlateral ovary		Radical	A, H, O, Lgh No		1	NED	237
124	IA	3	Mucinous	E	No	II Look	7	Pelvis-abdomen	Negative	Radical	A, H, O, T	Yes		DOD	15
125	IC5	1	Serous	E	Yes	–	45	Homolateral ovary		Conservative	A	Yes	Sterility	NED	101
126	IA	1	Serous	E	No	II Look	23	Homolateral ovary		Conservative	E	No		NED	69
130	IC[e]	2	Serous	A, end	No	Restaging	48	Skin	–	–	–	Yes		DOD	57
138	IC[f]	1	Serous	A, O	Yes	II Look	19	Controlateral ovary		Conservative	E	No	Sterility	AWD	24
140	IA	3	Clear cells	E	Yes	–	8	Pelvis-abdomen	Positive	Radical	A, H	Yes		NED	95
141	IA	1	Serous	E, O, Bps	No	–	61	Homolateral ovary		Conservative	A	No	1	NED	197
154	IC[e]	2	Endometrioid	E	Yes	Restaging	169	Homolateral ovary		Radical	A, H	Yes		NED	171
155	IA	3	Mucinous	A	Yes	Restaging	9	Lung	–	Conservative		Yes		DOD	13
164	IC[g]	1	Mucinous	A	Yes	II Look	25	Controlateral ovary		Radical	A, H	Yes		NED	86
179	IA	3	Endometrioid	A, O, Bps	Yes	II Look	7	Brain	–	–	–	No		DOD	9
1013	IA	1	Mucinous	E	Yes	II Look	11	Pelvis	Positive	Radical	BA, H	Yes		DOD	54
1024	IC[f]	3	Clear cells	E	Yes	II Look	6	Pelvis	Positive	Conservative	Bps	Yes		DOD	17
1029	IA	1	Mucinous	A, O, Bps	No	–	38	Pelvis-Abdomen	Positive	Radical	MA, H	No	1	DOD	43
1036	IA	2	Endometrioid	A	No	II Look	50	Pelvis	Negative	Radical	MA, H	Yes		NED	127
1037	IC[f]	3	Serous	A, O	Adjuvant	–	65	Nodes	Positive	Radical	MA, H	Yes		NED	208

[a]A, salpingo-oophorectomy; O, infracolic or total omentectomy; Bps, peritoneal biopsies; Lgh, lymphadenectomy; E, cyst enucleation; end, endometrial biopsy; H, hysterectomy; T, tumorectomy.
[b]II Look: post-chemotherapy surgery; Restaging: 3 months' restaging surgery.
[c]Platinum-based adjuvant chemotherapy.
[d]HED, no evidence of disease: AWD, alive with disease; DOD, dead of disease.
[e]Intraoperative cyst rapture.
[f]Capsule invasion.
[g]Positive cytology.

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Table 4. Univariate and multivariate analyses for recurrence-free survival and overall survival

Variable	Univariate			Multivariate[a]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Recurrence-free Survival						
Age (5 years' increment)	1.1	0.9–1.3	0.4	1.0	0.8–1.3	0.8
Grade (3 versus 1–2)	4.6	2.1–10.1	0.0001	4.2	1.5–11.7	0.0067
Adequacy surgical staging (no versus yes)	0.9	0.4–2.2	0.8	1.1	0.4–2.9	0.8
Stage (IC to II versus IA to IB)	1.3	0.6–2.6	0.5	0.9	0.4–2.0	0.8
Histotype (mucinous reference)						
Clear cells	2.6	0.6–12.4	0.2	0.5	0.1–2.6	0.4
Endometrioid	1.7	0.6–4.3	0.3	1.4	0.5–4.0	0.5
Serous	2.3	1.0–5.5	0.06	2.3	0.1–5.6	0.06
Overall survival						
Age (5 years' increment)	1.2	0.1–1.5	0.1	1.1	0.9–1.5	0.4
Grade (3 versus 1–2)	9.5	3.3–27.1	<0.0001	7.6	2.0–29.3	0.0032
Adequacy surgical staging (no versus yes)	0.9	0.2–3.1	0.8	1.0	0.3–4.1	0.9
Stage (IC to II versus IA to IB)	0.7	0.2–2.2	0.6	0.6	0.2–2.0	0.4
Histotype (mucinous reference)						
Clear cells	1.5	0.2–12.7	0.7	0.2	0.02–1.5	0.1
Endometrioid	1.1	0.3–3.9	0.8	0.7	0.2–3.1	0.7
Serous	0.7	0.2–2.9	0.7	0.7	0.2–2.9	0.7

[a]Adjuvant chemotherapic treatment was included in the multivariate model.

cystectomy, and 7 of 178, 4% for oophorectomy, Fisher's exact test *P*-value 0.49).

Univariate and multivariate analyses to determine possible factors that might influence RFS and OS were carried out (Table 4). Age, histotype, FIGO stage (we could not consider FIGO stage IB, as the number of patients was too small), adequacy of first surgery were not substantial at the univariate and multivariate analyses both for RFS and for OS. Adjuvant chemotherapy was an important prognostic factor for both RFS and OS in the univariate analysis, but not in the multivariate analysis. Grade of nuclear differentiation was significantly related to the prognosis of patients. In particular, since there was no statistical difference in terms of RFS and OS between patients with grade 1 and 2 tumors ($P = 0.09$ for OS and $P = 0.92$ for RFS), we considered these patients together and compared them with grade 3, which was found to be an important independent prognostic factor for RFS and for OS (RFS: HR: 4.2, 95% CI: 1.5–11.7, $P = 0.0067$; OS: HR: 7.6, 95% CI: 2.0–29.3, $P = 0.0032$, Table 4). Figure 2A and B show Kaplan–Meier curves for RFS and OS for patients with grade 3 tumors compared with those with grades 1–2.

All patients with an ovarian recurrence were rescued by second-line chemotherapy or surgery. Extraovarian relapse was significantly associated with a higher death rate (79% versus 0%, Fisher's exact test $P < 0.001$). All seven relapsing patients with poorly differentiated tumor and 7 of 20 (35%) with well- or moderately differentiated tumor had an extraovarian recurrence. Therefore, grade 3 tumors are significantly more likely to recur outside the pelvis (Fisher's exact test $P = 0.006$).

Obstetrical data after FSS were available for 231 patients; 8 were excluded because they relapsed within 1 year from the initial treatment and 1 had no available data. In all, 105 patients (45%) tried to become pregnant and 84 (80%) were successful. Sixteen had one or more spontaneous abortions. Therefore, 68 of 105 women (65%) had at least one child; 44 had only one child, 23 had two and 1 had three children after conservative treatment.

Univariate and multivariate analyses did not identify tumor-related factors affecting fertility. Increasing age (as 1 year increments) impaired the fertility potential (OR: 0.9, 95% CI: 0.8–1.0, $P = 0.018$). We found a close inverse correlation between tumor grade and attempt to become pregnant: significantly more patients with G1-to-G2 tumor tried to conceive compared with patients with G3 tumors (101 of 206, 49%, versus 4 of 25, 16%, Fisher's exact test $P = 0.002$).

discussion

Since FSS is considered a suboptimal treatment for EOC, we analyzed the oncological outcome of our patients. After a median follow-up of 9 years, the relapse rate in our population is 11%, which is similar to the majority of trials on early- stage EOC, treated with either a radical approach or FSS, where the relapse rate ranges between 4% and 15% (Table 1).

The grade of nuclear differentiation was the only determinant of relapse, as a quarter of our patients (24%) with a G3 tumor had recurrent disease. This is why some authors [6, 12] do not recommend FSS for patients with poorly differentiated tumors. The Fertility Taskforce of the European Society of Gynecologic Oncology (ESGO) has recently published recommendations about the conservative management of EOC [3], concluding that FSS should not be offered to patients with G3 tumors, though acknowledging that it is not possible to relate the worse prognosis of these patients to preservation of the ovary. However, the relapse rate in the subpopulation of patients with G3 tumors in our population was similar to the result reported

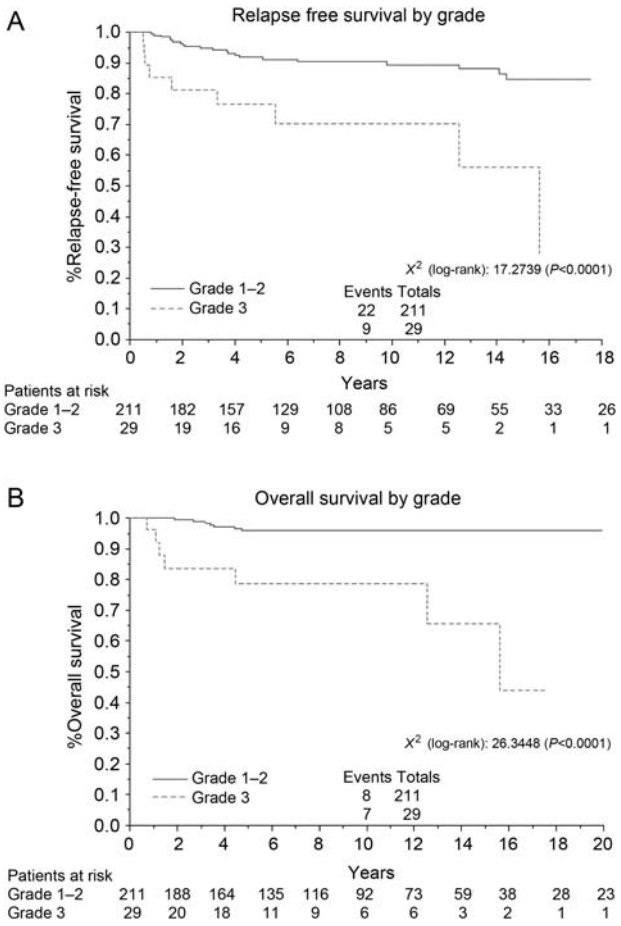

Figure 2. Kaplan–Meyer curve for (A) recurrence-free survival by grade and for (B) overall survival by grade.

in the ICON1/ACTION analysis in this subgroup (71 of 280, 25%), where all women underwent radical surgery and were then randomly assigned to receive or not adjuvant chemotherapy [15–18]. Therefore, FSS does not seem to raise the risk of relapse in G3 ovarian cancer patients.

However, it is already well-known that there are two distinct patterns of recurrence in patients who preserve the controlateral ovary, each of them associated to completely different prognoses. It is widely agreed that an ovarian recurrence can be successfully managed, in almost all cases, by surgery and/or chemotherapy, and patients with a recurrence only in the ovary rarely die of progressive disease. A distant recurrence, however, has a much worse prognosis, as it generally leads to death. This was confirmed in our population, as none of the patients with ovarian relapse died, compared with 79% (11 of 14) with distant metastases (Fisher's exact test $P < 0.001$). Our analysis found G3 was significantly associated with a distant relapse (Fisher's exact test $P = 0.006$) and a significantly lower OS. Our data suggest that the worse prognosis for grade 3 is probably related to the higher frequency of microscopic tumor localization beyond the ovary, which might explain the particular pattern of relapse of these tumors. All patients with G3 tumor were given conventional platinum-based chemotherapy regardless of FIGO stage and adequacy of first surgery, but this did not prevent distant relapses in seven cases.

The role of the adequacy of first surgery in our population deserves a comment, as it apparently did not influence the oncological outcome of patients. However, in the group of high-risk patients who received chemotherapy, we can note that relapse rate is considerably higher (20%) in patients inadequately staged than patients who had received an optimal staging/restaging surgery (10%) (supplementary Figure S1, available at *Annals of Oncology* online). We might hypothesize that a restaging surgery would have been mostly useful in these 55 patients, as some of them would have been probably upstaged and would not have met the criteria for a fertility-sparing approach. The reason why we did not carry out a restaging surgery was that they came to our attention after more than 3 months from first inadequate surgery, and we decided to treat them with chemotherapy before second-look surgery. In these patients, chemo might have hidden extraovarian localizations of the disease, which could have probably been the origin of the subsequent relapse.

Finally, cystectomy apparently led to the same oncological outcome as unilateral salpingo-oophorectomy. However, since the number of patients treated with this procedure is too small, it is not possible to draw any definitive conclusion about its safety and therefore it cannot be considered part of the standard conservative management.

These results, in our opinion, support the idea that FSS should be offered to all patients with EOC limited to the ovaries regardless of FIGO substage and tumor grade. Distant relapses are more frequent in patients with G3 tumors, though they can also occur in patients with well- and moderately differentiated tumors, but radical surgery will probably not reduce this risk, as suggested by Wright et al. [19] and, more recently, by Kajiyama et al. [20]. However, since we cannot exclude that the abdominal spread of the disease at recurrence in G3 patients might have started from the retained ovary, a closer follow-up is needed in this subgroup of patients.

There must be some feature in the biology of ovarian cancer that we have not understood yet, that explains the behavior of the tumor and that cannot be adequately predicted by any of the clinical and pathological parameters currently used, including the grade of nuclear differentiation, or overcome by conventional chemotherapy. A theory on the existence of two types of ovarian cancer which differ in aggressiveness and prognosis has been formulated by Kurman and Shih [21], and is supported by several distinctive molecular changes and genetic mutations in the two groups.

Our group already reported that cyclin E and minichromosome maintenance protein 5 (MCMP5) expression is an independent prognostic factor for stage I EOC patients [22]. We also recently reported that down-regulation of the expression in first-stage EOC of a particular family of microRNA, miR-200c, is associated with a worse prognosis regardless of clinical covariates, including histotype and grade [23], supporting that these tumors are phenotypically similar but molecularly different.

There might therefore be two distinct types of early-stage ovarian cancer that cannot be distinguished using clinical or pathological criteria. The grade of nuclear atypia is currently

the best predictor of the behavior of ovarian cancer, but its sensitivity and specificity are unsatisfactory in predicting recurrence and its pattern.

The last point to be discussed is the obstetrical outcome. The rate of successful pregnancies is encouraging, as 80% of patients who tried to conceive became pregnant, and 68 women had 93 live births. Chemotherapy did not seem to affect fertility, and no congenital abnormalities were observed. However, significantly fewer women with grade 3 tumor tried to conceive than grade 1–2 tumors. This might be explained by the fact that these patients are more conscious of being at higher risk of relapse and death. The choice of the conservative approach should be made after counseling and the gynecologist oncologist should clearly and honestly explain the risks to which patients are exposed and the benefits of retaining the reproductive tract, not only for preserving fertility, but also, as most of these patients are young, for the maintenance of their hormonal status and an intact body image. The risk of distant relapse is not related to the preservation of the genital tract, and the gynecologist oncologist should make every effort to avoid awareness of the risk of death—probably stronger in grade 3 patients—prevailing over the desire for pregnancy. Completion of surgery after childbearing can be proposed to patients, as relapses $\geq$10 years from the initial diagnosis are not infrequent and were observed in our population as well.

In conclusion, we urgently need to discover what molecular changes are responsible for distant relapses, for a better definition of the prognosis of each patient and possibly also to tailor therapy with more specific, molecular-targeted drugs. Until then, although our results have some limitation (retrospective non-randomized analysis, no centralized pathological review), it seems reasonable to take a conservative attitude toward young patients with early-stage EOC since ovarian recurrences, which are directly related to FSS, were always successfully managed and never led patients to death in our population. We believe that this risk is worth taking, as it is counterbalanced by a good pregnancy rate after treatment.

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disclosure

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