

Conservative surgery in stage I adult type granulosa cells tumors of the ovary: Results from the MITO-9 study

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HIGHLIGHTS

- About 30% of AGCTs are diagnosed in childbearing age and preserving fertility might be an issue.
- No difference in DFS was detected between patients undergoing unilateral salpingo-oophorectomy and radical surgery.
- A significantly worse DFS was found among patients undergoing cystectomy.
- Fertility sparing surgery in stage I AGCTs is safe, provided that cystectomy is avoided.

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ABSTRACT

Objective. About 30% of Adult type granulosa cell tumors of the ovary (AGCTs) are diagnosed in fertile age. In stage I, conservative surgery (fertility-sparing surgery, FSS), either unilateral salpingo-oophorectomy (USO) or cystectomy are possible options. The aim of this study is to compare oncological outcomes of FSS and radical surgery (RS) in apparently stage I AGCTs treated within the MITO group (Multicenter Italian Trials in Ovarian cancer).

Methods. Survival curves were calculated using the Kaplan-Meier method and compared with log-rank test. The role of clinicopathological variables as prognostic factors for survival was assessed using Cox's regression.

Results. Two-hundred and twenty-nine patients were included; 32.6% received FSS, 67.4% RS. In the FSS group, 62.8% underwent USO, 16.7% cystectomy, 20.5% cystectomy followed by USO. After a median follow up of 84 months, median DFS was significantly worse in the FSS-group (10 yr DFS 50% vs 74%, in FSS and RS group, $p = 0.006$). No significant difference was detected between RS and USO (10 yr DFS 75% vs 70%, $p = 0.5$). Cystectomy-group showed a significantly worse DFS compared to USO (10 yr DFS 16% vs 70%, $p < 0.001$). Patients receiving cystectomy and subsequent USO showed a better prognosis, even though significantly worse compared to USO (10 yr DFS 41% vs 70%, $p = 0.05$). Between FSS and RS, no difference in OS was detected. At multivariate analysis, FIGO stage IC and cystectomy retained significant predictive value for worse survival.

Conclusions. This study supports the oncological safety of FSS in stage I AGCTs, provided that cystectomy is avoided; USO should be the preferred approach.

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1. Introduction

Adult type granulosa cell tumors of the ovary (AGCTs) represent the most common tumor type among sex cord stromal tumors, and are characterized by an indolent course and late recurrences, with a reported recurrence rate as high as 64% [1–3]. Most of the diagnoses occur as stage I disease, and surgery represents the mainstay of treatment. Standard surgical approach consists in complete resection with total abdominal hysterectomy, bilateral salpingo-oophorectomy and complete surgical staging comprehensive of omentectomy and peritoneal biopsies [1–5]. Despite AGCTs are typical of perimenopausal or postmenopausal age, 30% of patients are diagnosed in childbearing age: for this subgroup preserving fertility might be an issue. In stage I disease, conservative surgery could be an option, considering that bilaterality has been reported only in 2–8% of all cases [5]. Fertility sparing surgery (FSS) consists in preservation of the uterus and at least one ovary with complete staging, along with endometrial sampling in order to rule out endometrial carcinoma [2,6–8]. Among conservative procedures for stage I AGCTs, either unilateral salpingo oophorectomy (USO) or cystectomy with the aim of preserving the remaining ovarian tissue, have been suggested [6–14]. Despite this, in the current literature the role of FSS is still controversial, with some authors reporting higher relapse and low survival rates [9,10,14,15]. In the study of Pautier et al. no relapses were detected among nine patients with stage IA AGCTs treated with RS, while three out of six patients treated with FSS recurred [15]. Similarly, in their series Lauszus et al. found a 10 year-survival rate of 40% and 90% in patients treated with FSS and RS, respectively [10].

Because of the rarity of this disease and the need of long term follow-up, no prospective randomized trials specifically addressing this and other surgical issues are currently available, and treatment modalities have been mainly assessed on the basis of retrospective series [7–14].

The current series represents the largest available specifically addressing the oncological safety of FSS compared to RS in apparently stage I AGCTs. The aim of this retrospective study was to evaluate the oncological safety of strategies of FSS compared to RS in apparently stage I AGCTs treated and followed up within the MITO group (Multi-center Italian trials in Ovarian cancer and gynecologic malignancies).

2. Patients and methods

Institutional review board approved the study. Patients' characteristics have been retrospectively reviewed for cases diagnosed from 1980 to December 2017. Patients with apparently stage I AGCT treated and followed up in a MITO center were included in the analysis. Patients referred to MITO group after receiving primary surgery elsewhere were also included. Patients' characteristics including age at diagnosis, clinical presentation, pathological details, intraoperative findings and surgical management at primary treatment and relapse along with follow up data were collected. Follow up data were collected until 30 November 2018.

All patients received up-front surgery. RS, consisting of bilateral salpingo-oophorectomy with or without hysterectomy was the standard of care when fertility was not an issue. FSS, either cystectomy or USO with sparing of the uterus was performed in patients with childbearing potential. Surgical staging was considered complete when including peritoneal washing, multiple peritoneal biopsies, omental biopsy and biopsy of any suspicious area. Some patients receiving cystectomy at primary surgery were subsequently candidate within four months to USO for oncological safety-issues. Pelvic and/or para-aortic lymphadenectomy were not standard procedures. Patients upstaged after secondary staging procedures or patients with documented bilateral tumors were excluded from the analysis. Tumors were staged according to International Federation of Gynecology and Obstetrics (FIGO) staging system of 2014 [17]. Reclassification of cases diagnosed prior to this new staging system was applied retrospectively evaluating surgical reports.

All pathological analyses were made by experienced gynecologic pathologists of MITO centers. In case of patients referred from centers outside the MITO group or challenging diagnoses, a central review in the coordinating center was requested.

Indication for adjuvant chemotherapy was not standardized among MITO centers and was therefore based on the single center's decision.

After being included in this study, patients were followed at MITO centers with a long-term schedule, comprising a periodic clinical, radiologic and serologic assessment.

Descriptive statistics were used to characterize the patient population. Clinicopathological features and treatment variables were evaluated for association with relapse and death. Follow up was assessed from the date of primary diagnosis to the date of last follow up visit. Disease free survival (DFS) was defined as the time period between first diagnosis to first observation of recurrence or the date last seen. Overall survival (OS) was defined as the time period from the date of initial diagnosis to the date of death or the date last seen.

Survival curves were calculated using the Kaplan-Meier method and were compared with the log-rank test to assess the statistical significance. Cox's regression model was used to analyze in univariate and multivariate analysis the role of clinicopathological factors as prognostic factors for survival. Differences were considered statistically significant at p value <0.05 . Hazard ratios were calculated for potential risk factor for relapse.

Statistical analysis was conducted using Statistical Package version 18.0 for Windows (SPSS, Inc., Chicago, Illinois).

3. Results

Two-hundred and twenty-nine patients with AGCTs were included in the study. Of these, 78 received FSS (32.6%), 161 RS (67.4%). Patients clinicopathological characteristics in the two cohorts of patients, according to surgical approach, are summarized in Table 1. Among

Table 1
Clinicopathological characteristics of patients according to surgical approach.

	All n, %	FSS n, %	RS n, %	p value
	239 (100%)	78 (32.6%)	161 (67.4%)	
Surgical procedures				
CYS	13 (16.7%)	13 (16.7%)	–	
CYS → USO	16 (20.5%)	16 (20.5%)	–	
USO	49 (62.8%)	49 (62.8%)	–	
Age (years)				
Median (IQR)	50.0 (41.0–59.0)	38.0 (31.0–42.0)	54.0 (48.0–63.0)	
Site of primary surgery				0.06
MITO center	158 (66.1%)	45 (57.7%)	113 (70.1%)	
Elsewhere	81 (33.9%)	33 (42.3%)	48 (29.8%)	
FIGO stage				0.19
IA	158 (66.1%)	47 (60.3%)	111 (68.9%)	
IC	81 (33.9%)	31 (39.7%)	50 (31.1%)	
Cyst rupture	63 (26.4%)	31 (39.7%)	32 (19.8%)	
Preoperative	18 (28.6%)	6 (19.4%)	12 (37.5%)	
Intraoperative	45 (71.4%)	25 (80.6%)	20 (62.5%)	<0.001
Complete staging	154 (64.4%)	37 (47.4%)	117 (72.6%)	
Adjuvant chemotherapy	24 (10.0%)	4 (5.1%)	20 (12.4%)	0.1
Relapse	58 (24.3%)	29 (37.2%)		
Site of relapse				
Pelvis	30 (12.6%)	17 (58.6%)	13 (44.8%)	
Peritoneum	6 (2.5%)	2 (6.9%)	4 (13.8%)	
Distant	9 (3.8%)	1 (3.5%)	8 (27.6%)	
Peritoneum and distant	6 (2.5%)	2 (6.9%)	4 (13.8%)	
Pelvic and peritoneum	7 (2.9%)	7 (24.1%)	0	

FSS: fertility sparing surgery; RS: radical surgery; CYS: cystectomy; USO: unilateral salpingo-oophorectomy; CYS → USO: cystectomy followed by unilateral salpingo-oophorectomy.

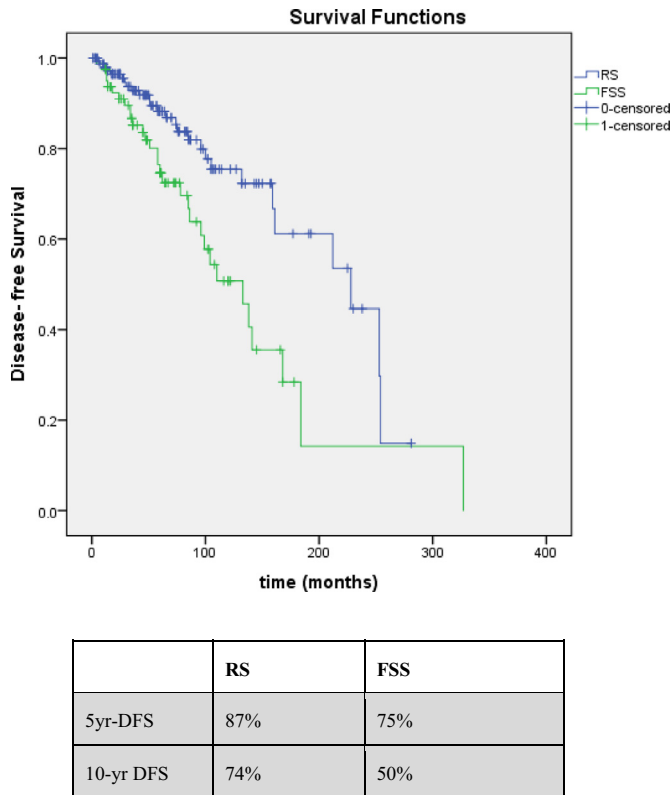
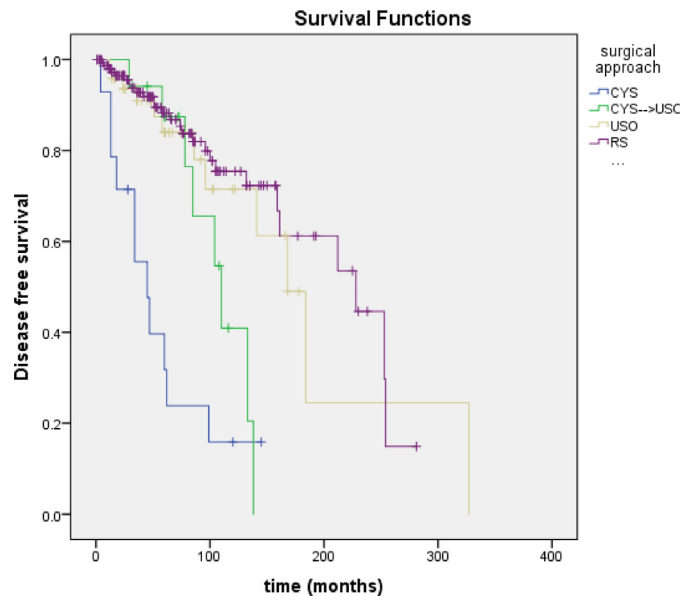


Fig. 1a. Disease-free survival according to type of surgery (FSS: fertility sparing surgery; RS: radical surgery).

patients receiving FSS, 49 (62.8%) underwent USO, 13 cystectomy (16.7%) and 16 cystectomy followed by USO (20.5%). Median age at diagnosis was 50.0 years (IQR 41.0–59.0) in the entire cohort, with patients in the FSS subgroup being significantly younger (median 38.0; IQR 31.0–42.0) than patients in the RS group (median 54.0; IQR 48.0–63.0; $p < 0.001$). In the whole cohort, 158 patients were stage IA (66.1%), 81 were IC (33.9%). One hundred and fifty-eight patients (66.1%) received primary surgery in a MITO center, the remaining 33.8% were treated elsewhere and subsequently referred for restaging, surgery for relapse or follow-up to MITO centers. As shown in Table 1, there was no statistically significant difference between FSS and RS groups regarding stage, site of primary surgery or administration of adjuvant chemotherapy. Only 10% of patients received adjuvant chemotherapy. The more common regimes were BEP (Platinum, etoposide, bleomycin) and carboplatin-paclitaxel combination. A significantly higher number of patients in the RS group received complete staging compared to FSS patients (72.6% vs 47.4%, $p < 0.001$).

As of December 30th 2018, median follow up was 84.0 months (IQR 35.0–110.0). During this period 58 patients (24.3%) experienced relapse of disease, and the median time from initial surgery to recurrence was 57.0 months (IQR 25.0–97.5). A significantly higher relapse rate was detected in FSS compared to RS group (37.2% vs 18.0%, $p = 0.001$). Regarding site of recurrence, distribution was significantly different between the two groups ($p < 0.001$), with 82.7% of recurrent patients in the FSS group experiencing at least a pelvic recurrence vs 44.8% in the RS subgroup.

As shown in Fig. 1a, DFS was significantly worse for patients undergoing FSS (10-yr DFS rate: 50% vs 74%, respectively, $p = 0.006$). When stratifying for the different surgical approaches of FSS (cystectomy and USO), interestingly there was no statistically significant difference in terms of DFS between RS and USO (10-yr DFS 73% vs 70%, $p = 0.5$).



	RS	USO	CYS→USO	CYS
5yr-DFS	87%	84%	82%	25%
10-yr DFS	75%	70%	41%	16%

Fig. 1b. Disease-free survival according to type of surgery (USO, unilateral salpingo-oophorectomy; CYS, cystectomy; CYS → USO, cystectomy followed by unilateral salpingo-oophorectomy).

Patients undergoing cystectomy showed a significantly worse DFS compared to RS (10-yr DFS rate: 16% vs 75%, $p < 0.001$) and USO (10-yr DFS rate: 16% vs 70%, $p < 0.001$) (Fig. 1b). On the other hand, patients first treated with cystectomy and subsequently subjected to USO showed an improved prognosis compared to cystectomy only, even though significantly worse compared to RS (10-yr DFS rate: 41% versus 75%, respectively, $p = 0.01$) or USO (10-yr DFS: 41% versus 70%, respectively, $p = 0.05$).

Deaths were documented in 5 patients (3 deaths of disease, and 2 for other causes). As shown in Fig. 2, considering only disease-specific OS, no statistically significant difference was detected between the two groups (10-yr OS rate: 98% for RS, versus 97% for FSS, $p = 0.8$).

Univariate and multivariate regression analyses were performed in order to assess the influence of different clinicopathologic characteristics and treatment approaches on DFS. As shown in Table 2, among all variables, age < 50 years, surgery carried out elsewhere, stage IC, fertility preserving surgery, adoption of cystectomy, and incomplete staging were directly associated with worse prognosis; on the other hand, administration of adjuvant chemotherapy was shown not to have prognostic role.

At multivariate analysis only FIGO stage IC and surgical approach with cystectomy retained significant predictive value for worse survival.

4. Discussion

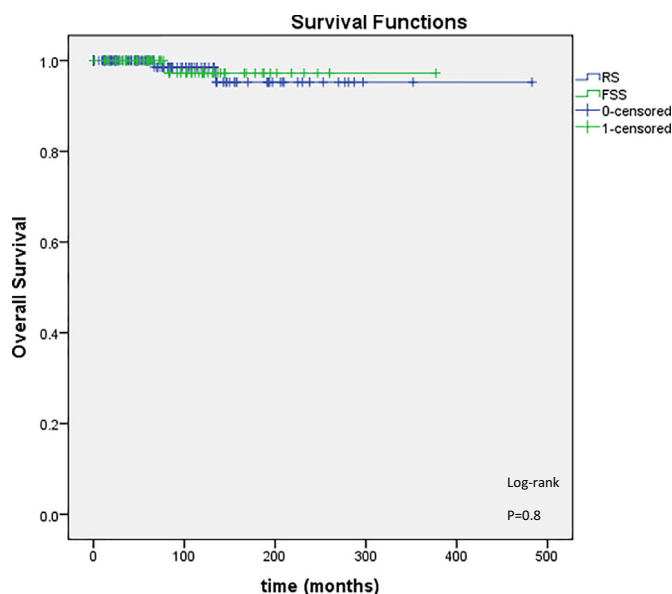
To our knowledge, the current series is the largest available specifically addressing the oncological safety of FSS compared to RS in stage I AGCTs.

Two large cohort studies have suggested that conservative surgery could be feasible, as no significant difference with RS was detected in terms of survival [12,13]. However, in the first study 83 sex cord stromal tumors, including both Sertoli-Leydig and GCTs, were considered together as a single cohort. Notably, only one patient underwent cystectomy, so almost all of the patients in the FSS subgroup received USO [12]. In the study by Lee et al., including 86 patients with stage I disease, only 3 patients in the FSS cohort (8.3%) received cystectomy [13]. Considering this, the results of these studies are in line with ours, as we also found no statistically significant difference between USO and RS. Another recently published study included a total of 113 patients with AGCTs, 61 undergoing FSS. Of these, 7 patients (11.4%) received cystectomy. Type of surgical approach (FSS vs RS) was significantly associated with DFS in univariate but not in multivariate analysis. Interestingly they found significant differences in DFS between USO and cystectomy, with relapses detected in 6 of the 7 patients who have received cystectomy (85.7%) [14]. A comparable result has been found in our series with 10/13 (76.9%) patients in the cystectomy group experiencing recurrent disease.

None of the above mentioned series reported the survival rates of patients first undergoing cystectomy and, once received the confirmation of AGCT, subsequent USO. In our series, patients in this subgroup showed a significant survival advantage compared to patients receiving only cystectomy (5 yr DFS 82% vs 43%, $p = 0.05$).

Previous reports from the MITO group had found no difference between FSS and RS [18,19]. However, those studies included patients diagnosed from 1965 to 2008 and did not distinguish the type of conservative approach: an important proportion of patients only received USO as an option for FSS, as ultraconservative surgery with cystectomy was fairly uncommon. Ultraconservative surgery has been gaining an increasing role in gynecological oncology in the last two decades: the current series adds on the 10-year experience from the MITO group and, to note, most of the patients treated with cystectomy have been diagnosed after 2005, thus potentially slightly modifying the previously reported results.

With the known limits of a retrospective and multicenter study, these data, derived from the largest series available regarding this specific issue, support the oncological safety of FSS in GCTs, provided that



	RS	FSS
5yr-OS	100%	100%
10-yr OS	98%	97%

Fig. 2. Overall survival according to type of surgery (FSS: fertility sparing surgery; RS: radical surgery)

any attempt to perform cystectomy is avoided. Considering that GCTs originates from the ovarian stroma, a clear cleavage between the tumor and remaining ovarian tissue is difficult to be identified, leading to ineffective removal of tumor, spread of cancer cells within the abdominal cavity and therefore higher risk of relapse [14]. Interestingly, among patients treated with cystectomy, three had a relapse in the same ovary and 4 in the contralateral ovary (Table 3). Since AGCTs are often incidentally diagnosed upon a presumed benign cyst, in case ultraconservative surgery has been performed, patients desiring to preserve their fertility should be addressed to surgical restaging with USO. Fresh frozen intraoperative analysis plays an important role in the management of these cases. Notably, surgical approach (laparoscopy vs open surgery) has already been documented not to influence prognosis, provided that the procedure is performed by an experienced surgeon [20].

Table 2
Prognostic value for DFS in stage I AGCTs.

Characteristics	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age (years)		
<50 vs ≥50	2.36 (1.35–4.11)	–
Center		
Elsewhere vs MITO	2.96 (1.69–5.20)	–
Stage		
IC vs IA	3.99 (2.29–6.95)	6.21 (2.49–15.46)
Surgery		
FSS vs RS	2.13 (1.25–3.64)	–
Cystectomy vs others	3.41 (1.54–7.53)	4.21 (1.85–9.58)
Staging		
Incomplete vs complete	2.03 (1.16–3.55)	–
Adjuvant chemotherapy		
Yes vs no	0.82 (0.39–1.72)	–

FSS: fertility-sparing surgery; RS: radical surgery.

Table 3

Clinical characteristics of relapsing patients in the cystectomy group.

Patient	Age	Stage	Complete staging	ADJCT	DFS (months)	Site of recurrence	Treatment	Number of subsequent relapses	Outcome
1	37	IA	No	No	60	Contralateral ovary	Surgery + CT	1	NED
2	38	IC	No	No	62	Ipsilateral ovary	Surgery + CT	4	NED
3	41	IA	No	No	45	Pelvis	Surgery + CT	3	AWD
4	31	IC	No	No	13	Ipsilateral ovary, peritoneum	Surgery + CT	1	NED
5	33	IC	No	No	47	Pelvis	Surgery + CT	1	AWD
6	29	IC	No	No	18	Peritoneum	Surgery + CT	4	AWD
7	27	IC	Yes	No	4	Ipsilateral ovary	Surgery + CT	0	NED
8	30	IC	No	No	99	Contralateral ovary	Surgery	0	NED
9	30	IC	Yes	No	34	Contralateral ovary, pelvis	Surgery + CT	2	NED
10	32	IC	No	No	86	Contralateral ovary, peritoneum	Surgery + CT	0	NED

CT: chemotherapy; AWD: alive with disease; NED: no evidence of disease.

The results of the present study suggest that OS is not affected by the surgical strategy chosen at primary surgery, as most of the recurrences occur later on in the course of the disease and are effectively treated with surgery. Nevertheless, quality of life of these patients is surely hampered, as most of them experience subsequent relapses requiring repeated surgeries and chemotherapy lines (Table 3).

This study presents some limitations, that are often found in multicenter retrospective studies on rare diseases. First, its retrospective nature might be a source of selection bias. The two groups (FSS and RS) were well balanced in terms of adjuvant chemotherapy and stage distribution. Surgical staging, however, was not systematically offered to all patients receiving FSS, and this might potentially affect our results. Second, centralized pathology review was not routinely performed, but reserved to patients referred to MITO centers after primary surgery or for challenging cases. Despite this, all cases were diagnosed by experienced gynecological pathologists dedicated to gynecologic oncology.

Despite these limitations, the present experience is the largest available in literature including patients with apparently stage I AGCTs, specifically assessing the oncological safety of FSS in this setting.

5. Conclusions

Results from this study support the oncological safety of a conservative approach in apparently stage I AGCTs, provided that cystectomy is avoided. In these cases removal of the entire ovary should be the preferred approach. As stated during the last Ovarian Cancer Consensus Conference of the Gynecologic Cancer Intergroup (GCG), international collaborations in the setting of rare tumors should be implemented to support the consistency of these results [21].

Author contributions

AB and GM developed the concept of the study. All authors enrolled patients and provide information regarding follow up. AB and GF performed statistical analyses. AB drafted the paper, with the support of GM, LB, GF, DL, GC, UDG, GG. All authors critically reviewed and revised the manuscript. All authors finally approved the final version.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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