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ORIGINAL ARTICLE

The role of staging and adjuvant chemotherapy in stage I malignant ovarian germ cell tumors (MOGTs): the MITO-9 study

G. Mangili[1], C. Sigismondi[1*], D. Lorusso[2], G. Cormio[3], M. Candiani[1], G. Scarfone[4], F. Mascilini[5], A. Gadducci[6], A. M. Mosconi[7], P. Scollo[8], C. Cassani[9], S. Pignata[10] & G. Ferrandina[11]

[1]Department of Gynecology and Obstetrics, I.R.C.C.S. San Raffaele Hospital, Milan; [2]Department of Gynecologic Oncology, IRCCS Foundation National Cancer Institute, Milan; [3]Department of Biomedical Science and Human Oncology, University of Bari, Bari I, Bari; [4]Department of Obstetrics, Gynecology and Neonatology, IRCCS Fondazione Cà Granda, Ospedale Maggiore Policlinico, Milan; [5]Gynecology Oncology Unit, Foundation "PoliclinicoUniversitario A. Gemelli", Rome; [6]Division of Gynecology and Obstetrics, Department of Experimental and Clinical Medicine, University of Pisa, Pisa; [7]Azienda Ospedaliera Universitaria Perugia, Perugia; [8]Department of Obstetrics and Gynecology, Cannizzaro Hospital, Catania; [9]Department of Obstetrics and Gynaecology Fondazione IRCCS Policlinico San Matteo—University of Pavia, Pavia; [10]Department of Urology and Gynecology, Istituto Nazionale Tumori "Fondazione G. Pascale" IRCCS, Naples; [11]Department of Medicine and Health Science, University of Molise, Campobasso/Foundation, PoliclinicoUniversitario A. Gemelli, Rome, Italy

Correspondence to: Dr Cristina Sigismondi, Department of Gynecology, IRCCS San Raffaele Hospital, Via Olgettina, 60, 20132 Milano. Tel: +39-0226433470; Fax +39 0226432759; E-mail: sigismondi.cristina@hsr.it

Background: Surgery followed by platinum-based chemotherapy is the standard of care for MOGCTs, except for stage IA dysgerminoma and stage IA grade 1 immature teratoma where surveillance only is recommended. The role of adjuvant chemotherapy and surgical staging is debated.

Patients and methods: Data from 144 patients with stage I MOGTs were collected among MITO centers (Multicenter Italian Trials in Ovarian Cancer) and analyzed.

Results: Fifty-five (38.2%) patients were affected by dysgerminomas, 49 (34%) by immature teratomas, 26 (18.1%) by yolk sac tumors and 14 (9.7%) by mixed tumors. Seventy-three (50.7%) patients receive surgery plus chemotherapy, while 71 (49.3%) patients underwent surgery alone. The latter group included 32 dysgerminomas (14 IA–13 Ix, 3 IB, and 2 IC), 34 immature teratomas (20 1A–13 IA grade 1, 6 Ix, 1 IB, and 7 IC), 4 mixed tumors and 1 yolk sac tumor. Forty-four patients did not received chemotherapy, even if it would have been indicated by recommended approach. 94 (65.3%) patients received peritoneal surgical staging. Twenty-three (15.9%) developed a recurrence. Incomplete surgical staging was associated with recurrence ($P < 0.05$; OR 2.37) at Cox regression analysis. Seven patients died. Four patients were affected by yolk sac tumors, two by mixed tumors and one by immature teratoma. Five patients died for disease, one for acute leukemia and one for suicide. Prognostic parameter analyses showed that yolk sac component is a predictor for survival ($P < 0.05$). Five-years OS rates were 96.8% and 88.7% in the surgically staged and the incomplete staged group, respectively, while 93.8% and 94.1% in the standard treatment and in the surveillance group, respectively.

Conclusions: This study shows that surveillance seems not to affect survival; chemotherapy should be reserved for relapse resulting in high cure rate. Incomplete peritoneal surgical staging is associated with recurrence. Yolk sac histology worsens the prognosis.

Key words: malignant germ cell ovarian tumors, adjuvant chemotherapy, surveillance

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare ovarian tumors that account for 2%–5% of all ovarian malignancies [1]; they usually occur in young women, are often unilateral, and diagnosed at an early stage of disease [2]. MOGCTs consist of several different histological types, all deriving from primordial germ cells of the ovary [3] and are characterized by high chemosensitivity, thereby allowing high chance of cure, with almost 100% overall survival in early stage disease [4, 5].

Due to their rarity, relatively few studies have focused on female MOGTs patients, whose treatment is, therefore, mainly mutuated from guidelines for management of male MOGGTs and epithelial ovarian cancer [4, 6, 7].

Currently, the standard of care includes fertility-sparing surgery with comprehensive surgical staging (CSS) followed by platinum-based chemotherapy with the exception of stage IA dysgerminoma and stage IA grade 1 immature teratoma, for which surgery alone can be considered as curative [8, 9].

However, while CSS is recognized as the mainstay of treatment in epithelial ovarian cancer, only investigators have addressed its role in MOGTs, suggesting equivalent clinical outcome between CSS and not completely staged patients [10]; moreover, criticisms have been raised about the need to continue with the practice of excising the greater omentum, and retroperitoneal lymph nodes in the absence of visible disease [4, 10–12].

There is also growing scientific interest in the safety of using post-resection surveillance for a much broader group of patients: given that the effectiveness of adjuvant chemotherapy in early stage MOGTs has been not entirely clarified [13], while acute and late side effects associated with the most commonly used platinum based regimens are well acknowledged [14].

Therefore, selection of features able to accurately identify cases who could be managed without chemotherapy after surgical management, considering also that postponing treatment to the salvage setting may not be detrimental for overall survival given the very high chemosensitivity of this disease [15].

The aim of this study was to investigate the role of surgical staging and adjuvant chemotherapy in a large series of stage I MOGTs patients treated at the MITO (Multicenter Italian Trials in Ovarian cancer) Group centers.

Patients and methods

The MITO-9 study is an Italian, multicentric, retrospective collection of clinic-pathological characteristics and treatment details of rare ovarian tumors. We report a series of 144 patients with a diagnosis of stage I germ cell tumor of the ovary who were evaluated and treated at MITO centers between 1982 and 2014.

Institutional Review Board approved the study. Patient data were collected into a database recording information about age at diagnosis, type of clinical presentation, tumor markers, surgical details, stage, histology, adjuvant chemotherapy, relapse characteristics, salvage therapy and follow up. Histological type was defined according to the classification of the World Health Organization. Patients affected by immature teratomas, dysgerminomas, embryonal carcinomas, yolk sac tumors and mixed germ cell tumors were included in the study. Immature teratoma was graded according to the criteria developed by Norris et al. [16] and modified by Robboy and Scully [17]. Patients were staged according to the FIGO classification of ovarian tumors [18]. Patients who did not receive surgical staging were classified as stage Ix.

Surgery was the first treatment for all patients. A fertility sparing operation was defined as the preservation of the uterus and one ovary to maintain fertility. Hysterectomy and bilateral salpingo-oophorectomy was classified as "radical surgery". Peritoneal biopsies, omentectomy or omental biopsy, and peritoneal washings were classified as 'peritoneal staging' with or without retroperitoneal lymph node biopsy or excision. Fifty-one patients were operated on outside a MITO center and were then referred to MITO centers in the postoperative setting for subsequent evaluation.

Specific indication for administration of adjuvant chemotherapy in stage I MOGTs are not standardized among MITO centers; therefore, the decision to administer adjuvant chemotherapy in this setting of patients was made by the attending physicians of each center after discussion with patients.

Postoperative chemotherapy was represented by cisplatin, etoposide and bleomycin every 3 weeks for three or four courses (BEP). Patients were followed-up by periodic clinical, serologic and radiologic evaluation: follow-up included pelvic examination and evaluation of tumor markers every 3 months for the first 2 years and every 6 months during years 3–5 or until progression was documented. Pelvic and abdominal ultrasound was performed every 6 months, whereas computed tomography of the abdomen and pelvic was performed yearly. Relapse was defined with tumor mass.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. Median follow-up period was measured from the date of primary surgery to the time of last follow-up visit. Disease-free survival (DFS) was defined as the time between diagnosis and evidence of relapse, or date last seen. Overall survival (OS) was defined as the time from the date of initial diagnosis to the date of death by any cause, or the date last seen.

Overall survival and disease-free survival curves were constructed using Kaplan–Meier method and were compared with the log-rank test.

Cox's regression model was used to analyze the role of clinic-pathological and treatment parameters as prognostic factors for disease free survival and overall survival. All P values were 2 sided. Differences at P value <0.05 were considered statistically significant.

Statistical analysis was performed with SPSS Statistical Package version 18.0 for Windows.

Results

Between 1982 and 2014, 144 patients affected by stage I germ cell ovarian tumors were referred or treated at MITO centers.

One hundred patients (69.4%) were nulliparous; 107 (74.3%) patients presented with abdominal pain and/or pelvic mass; and in 7 cases (4.9%), the tumor was revealed by the abrupt onset of acute abdomen.

As shown in Table 1, 55 patients (38.2%) were affected by dysgerminoma, while 49 patients (34.0%) and 26 patients (18.1%) were diagnosed with immature teratoma and yolk sac tumor, respectively. Only 14 cases (9.7%) had mixed tumors, which included a component of yolk sac tumor.

Mean age at diagnosis was 27.5 years (median age: 27, range 9–76). Mean age was 26, 26, 28, and 30 for dysgerminoma, mixed tumors, immature teratoma and yolk sac, respectively.

Overall, 55 patients (38.2%) had stage IA disease, while 5 patients (3.5%) and 47 (32.6%) patients were stage IB and IC disease, respectively; 37 patients (25.7%) were classified as stage Ix.

Surgery was the first treatment for all patients. Ninety-three patients (64.6%) were operated at MITO centers, while 51 (35.4%) were referred after surgery. The vast majority of patients

Table 1. Clinico-pathological patient features and treatment strategies

Clinico-pathological characteristics		Stage	No. (%)
Histology	Dysgerminoma (*N*=55)	IA	18 (12.5)
		IB	3 (2.1)
		IC	16 (11.1)
		Ix	18 (12.5)
	Immature teratoma (*N*=49)	IA	22 (15.3)
		IB	2 (1.4)
		IC	12 (8.3)
		Ix	13 (26.5)
	Yolk sac tumors (*N*=26)	IA	10 (6.9)
		IC	13 (9.0)
		Ix	3 (2.1)
	Mixed (*N*=14)	IA	5 (3.5)
		IC	6 (4.1)
		Ix	3 (2.1)
Treatmentstrategies			
Site of primary surgery	MITO centers		93 (64.6)
	Elsewhere		51 (35.4)
Surgical treatment	Fertility sparing		125 (86.8)
	Radical surgery		19 (13.2)
Peritoneal staging	No		50 (34.7)
	Yes		94 (65.3)
Lymph node staging	No		99 (68.7)
	Yes		45 (31.2)
Adjuvant chemotherapy	No		71 (49.3)
	Yes		73 (50.7)
Total			144 (100)

Table 2. Cox's regression analysis of risk factors for recurrence

Factor	*N.*	Recurrence rate (%)	*P* value (Cox regression)	OR 95% CI
Fertility sparing	21	16.8	0.353	1.99 (0.46–8.55)
Radical surgery	2	10.5		
Adjuvant chemotherapy	9	18.6	0.209	1.71 (0.74–3.95)
Surgery alone	14	12.2		
Standard treatment	12	10	0.117	1.93 (0.84–4.4)
Surveillance	11	25.6		
Peritoneal staging	**10**	**8.6**	**0.04**	**2.37 (1.04–5.44)**
No staging	**13**	**26**		
Stage IA–IB	12	13	0.144	1.87 (0.8–4.32)
Stage IC	11	21.1		
Yolk sac/mixed	5	17.1	0.439	1.48 (0.55–3.98)
Other histologies	18	12.8		

Peritoneal staging versus No staging is the only independent risk factor for recurrence ($P<0.05$).

underwent fertility-sparing surgery ($n=125$, 86.8%), while 19 patients underwent radical surgery (including five postmenopausal patients, five cases who had already completed their childbearing plans, two patients had bilateral tumors pathologically defined and four cases affected by gonadal dysgenesis; in the remaining three cases, the reason was unknown). Complete peritoneal surgical staging was carried out in 94 patients (65.3%), while lymph node staging was performed in 45 cases (31.2%), and 20 of which, 20 had dysgerminoma.

In the whole series, adjuvant chemotherapy was administered to 73 patients (50.7%); supplementary Table S1 (available at *Annals of Oncology* online) shows the distribution of patients affected by MOGTs according to adherence to the recommended treatment approach for adjuvant chemotherapy administration.

In the dysgerminoma group, 33 out of 55 patients (60.0%) were treated as recommended; in particular, 14 out of 18 stage IA patients (77.8%) were not administered the recommended adjuvant chemotherapy, and only 19 out of 37 (51.3%) patients received chemotherapy according to the recommended treatment approach.

Conversely, 28 (57.1%) out of 49 patients with immature teratomas received the recommended treatment: in particular, all stage IAG1 patients underwent surveillance, while only 15 out of 36 patients (41.7%) who should have received adjuvant treatment, were really treated.

All patients with yolk sac tumor underwent adjuvant chemotherapy as recommended, with the exception of one case who refused treatment.

Finally, 10 (71.4%) out of 14 patients affected by mixed tumors received the recommended adjuvant chemotherapy.

Overall, 44 patients did not receive chemotherapy even if it would have been indicated by the recommended treatment approach.

Patient outcome

Median follow-up period was 59 months (range: 6–345 months).

Recurrence of disease occurred in 23 patients (16.0%) whose main features are summarized in supplementary Table S2 (available at *Annals of Oncology* online): relapse of disease was documented in 7 out of 55 patients affected by dysgerminoma (12.7%), in 11 out of 49 immature teratomas (22.4%), in 3 out of 26 patients affected by yolk sac tumor (11.5%) and in 2 out of 14 mixed tumor (14.2%).

Table 2 shows Cox regression analyses performed to evaluate the influence of different clinico-pathological characteristics and treatment strategies on rate of recurrence.

Incomplete surgical staging was statistically associated with a high risk of recurrence.

At relapse, 19 patients (82.6%) received salvage surgery, which was followed by postoperative chemotherapy in 10 patients; 1 patient underwent only diagnostic laparoscopy, and salvage chemotherapy only was administered to 3 patients.

In the whole series, there were five deaths from MOGTs, one patient (stage IC mixed tumor treated by surgery plus PEB) died because of acute leukemia 2 years after the end of treatment, and one patient (stage IC yolk sac tumor treated by surgery plus PEB) committed suicide.

Moreover, two patients developed a second malignancy (one case of melanoma occurring 12 years after MOGT diagnosis, and one case of breast cancer) which was treated to complete remission and remain free of disease.

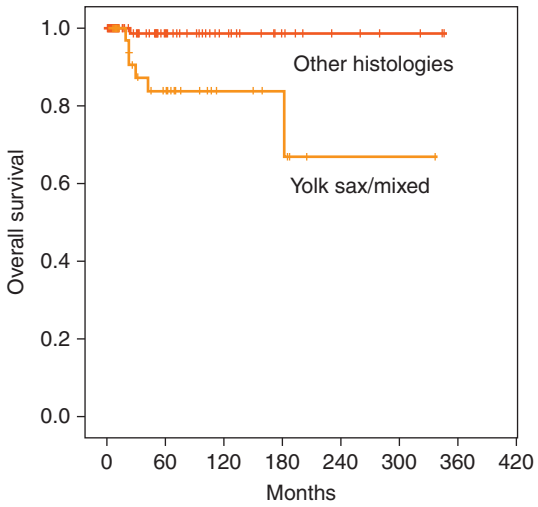

Figure 1. OS in yolk sac tumors/mixed versus other histologies.

As far as overall survival is concerned, the presence of yolk sac/mixed tumor played a major role compared to other histologies (Figure 1): in particular, 5-years OS rate was 83.7% in patients bearing yolk sac/mixed tumors versus 98.6% patients with other histotypes (P value <0.05). Conversely, the extent of surgical staging seemed not to affect prognosis (5-years OS rate = 96.8% and 88.7% in complete versus incomplete surgical staging, respectively). The administration of adjuvant treatment (5-years OS rate= 93.7% and 94.2% in the chemotherapy group versus the not treated group), stage (5-years OS rate= 90.8% and 95.6% in the stage IC versus others stage I), and fertility sparing surgery (5-years OS rate= 93.1% and 100% in the fertility sparing versus the radical surgery group) were shown not to worsen the prognosis. The 5-year OS was 93.8% and 94.1% in the standard treatment and in the surveillance group, respectively.

Multivariate analysis of parameters predicting OS showed that the presence of yolk sac component retained its independent unfavorable prognostic role, while administration of adjuvant treatment, stage IC, type of surgery and peritoneal staging did not correlate with patients outcome.

Discussion

To our knowledge, this is the largest study focusing on the role of completeness of surgical staging and administration of adjuvant chemotherapy in stage I MOGTs; indeed, one of the challenges in the optimal management of this disease is to identify the groups of patients, according to different histotypes and stages, who really benefit from chemotherapy and to avoid chemotherapy in patients that are cured by surgery alone.

MOGTs have been largely studied as a unique category but they represent a heterogeneous group of neoplasms with variable biological behavior, clinical presentation and prognosis. The low incidence of malignant ovarian germ cell tumors represents a limitation to detect significant differences in the distinct entities even in this study.

Several studies have explored the issue of the feasibility of surgery followed by surveillance: in particular, Bonazzi et al. [19] reported 22 patients with stage I grade 1–2 immature teratoma treated by surgery alone: two patients developed recurrence of disease and were salvaged with repeat surgery. Dark et al. [20] enrolled 24 patients affected by stage IA MOGT (9 patients with dysgerminoma, 9 with immature teratoma and 6 with yolk sac tumor) into a surveillance strategy; two patients experienced recurrences and both were completely cured at relapse, while one died of pulmonary embolus during chemotherapy. Mitchell et al. [21] reported only one relapse in nine patients with stage I non-dysgerminomatous germ cell tumors salvaged by surgery.

Two studies from the Pediatric Oncology Group showed the feasibility of surveillance in 44 patients affected by immature teratoma (31 pure and 13 with yolk sac elements). There was only one recurrence which was cured and the overall survival was 100% [22, 23].

Two other studies reported a total of 39 patients with stage I MOGTS treated with surgery alone, with an overall survival of 97.4% [24, 25]. Patterson et al. [26] questioned the need to use potentially toxic chemotherapy in a retrospective review of 37 patients with stage I MOGTs treated with surgery alone. They found a relapse rate of 36% and 22%, respectively, in the non-dygerminomatous and the dysgerminomatous group. Only one patient died of chemoresistant disease, proving the surveillance approach could be safe [26]. We also have reported the feasibility of surveillance in stage I G2-3 immature teratoma: indeed, the relapse rate was 21% in surveillance patients, but the overall survival was 100% [5]. Moreover, a recent report from the Malignant Germ Cell Tumor International Collaborative questioned the utility of adjuvant chemotherapy in stage I immature teratoma (regardless the grading of disease) because it did not decrease relapses in a combined and harmonized pediatric and adult cohort [27].

In the current dataset, 44 patients avoided adjuvant chemotherapy (surveillance group) and 9 patients needed chemotherapy at relapse: 35 patients avoid unnecessary chemotherapy that would have been administrated according to the standard guidelines.

Incomplete peritoneal surgical staging was a risk factor for recurrence at Cox regression analysis. Twenty-six percent of relapsed patients had not received complete peritoneal surgical staging (recurrence rate: 8.6% versus 26% in the surgically staged and the unstaged group, respectively). The need for comprehensive surgical staging that accompanies removal of gross disease has been debated. Billmire et al. [4] proposed a surgical staging including complete resection of the tumor-containing ovary with sparing of the fallopian tube, inspection and palpation of contralateral ovary, omentum, lymph nodes and peritoneal surfaces with biopsy of any suspicious lesion or lymph nodes and collection of peritoneal washing. Liu et al. [10] reported that a clinical intraoperative exploration was safer and more effective than comprehensive surgical staging in a population of 92 patients affected by MOGTS. Of note, in this dataset, all patients but one, received adjuvant chemotherapy [10]. In a previous study, we reported that patients affected by unstaged IA pure ovarian dysgerminoma could received either surveillance or restaging reserving chemotherapy to relapse with excellent outcome (100% OS) [6]. Recently, Billmire et al. [15] evaluated the impact of central surgical review in a study on malignant germ cell tumors: the highest rate of discordance was documented in stage I ovarian tumors, with 34% of patients with stage I resulting at a more advanced

stage or failing to meet stage definition; the event-free survival was 57% in patients not upstaged after central review and 25% in those who did not meet criteria for stage I [15]. Appropriate assignment of stage allows timely chemotherapy for those patients diagnosed with greater than stage I and allows an appropriate evaluation of disease related events for a better comparison between published series. However, while peritoneal surgical staging resulted in a lower recurrence rate, it did not improve the overall survival, underscoring the high chemosensitivity of the disease; several studies have reported higher recurrence rate for surgical unstaged stage I MOGTs, although the survival rate remains excellent [8, 28]. Even in our dataset, the unstaged patients presented a higher rate of recurrence but an excellent prognosis and this aspect raises a question that in our opinion should be discussed with the patient whether is better to receive an immediate laparoscopic surgical restaging or salvage chemotherapy at the time of relapse. Yolk sac histology has been already reported as a poor prognostic indicator [28, 29]. In our dataset, only one patient affected by IC unstaged yolk sac did not receive chemotherapy because of patient refusal, and experience recurrence and death of disease.

In the literature, we are aware of no studies specifically addressing the role surveillance in young adults with yolk sac tumors. Previous literature reported on 17 patients with stage IA germ cell ovarian tumors with a yolk sac component who were treated using surgery and surveillance; five patients experienced relapse and all were successfully treated by salvage chemotherapy [5]. The Children's Oncology Group reported on 25 patients affected by stage I ovarian germ cell tumors (with yolk sac as predominant histology) enrolled in a surveillance program: 11 out of 12 patients who experienced relapse received successful salvage chemotherapy and OS was preserved. However, four not completely staged had FIGO IC disease, underlining that probably the recurrence rate would be lower for IA patients [15].

In conclusion, our study shows that surveillance should be performed in stage I dysgerminoma and immature teratoma tumors with correct surgical peritoneal staging. If surgical staging procedures have not been performed, surveillance could however be an option.

In yolk sac and mixed histologies with yolk sac elements, surveillance could be evaluated in stage IA completely surgically staged patients with normalized alfa feto protein value after surgery, while it should be avoided if surgical staging had not been performed because postponing chemotherapy in this more aggressive histology may worsen the prognosis. These observations confirm the possibility to identify a subset of MOGTs patients who can be spared the risk of acute and late morbidity and mortality associated with chemotherapy in long term survivors [30]. Indeed, we also documented one case of malignant melanoma and one case of breast carcinoma occurring after MOGTs treatment, as well as 1 death due to acute leukemia that could be a late effect of etoposide.

The main limitation of this study is that is a retrospective dataset and firm conclusions cannot be made. The approach that could usefully be examined in future might be a lower adjuvant chemotherapy schedule in the high-risk subsets of low stage disease, seeking to avoid recurrence and the need for more intensive treatment at that time. Moreover, follow-up schedules should be tailored to risk, timing and the nature of recurrence. Another limitation of this study is that the cohort is probably incomplete because not all MITO centers sent data about all patients affected by MOGTs and the centers that sent data probably did not send all cases.

Prospective studies are required to evaluate surveillance in adolescent and adult patients affected by yolk sac tumors.

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