Gynecologic Oncology 158 (20202020) 666–672

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Need for risk-adapted therapy for malignant ovarian germ cell tumors: A large multicenter analysis of germ cell tumors' patients from French TMRG network

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HIGHLIGHTS

- Malignant ovarian germ cell tumors are rare tumors.
- French Rare Malignant Gynecological Tumors Network collect data about these tumors.
- Adjuvant chemotherapy for stage I does not seem to improve survival.
- Active surveillance can be proposed for selected patients.
- Risk-adapted treatment should be assessed on a prospective basis at European level.

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https://doi.org/10.1016/j.ygyno.2020.06.491

ARTICLE INFO

Article history:
Received 15 April 2020
Accepted 12 June 2020
Available online 3 July 2020

Keywords:
Rare malignant ovarian tumors
TMRG
Prognostic factors
Stage I

ABSTRACT

Background. Malignant ovarian germ cell tumors are rare tumors, affecting young women with a generally favorable prognosis. The French reference network for Rare Malignant Gynecological Tumors (TMRG) aims to improve their management. The purpose of this study is to report clinicopathological features and long-term outcomes, to explore prognostic parameters and to help in considering adjuvant strategy for stage I patients.

Patients and methods. Data from patients with MOGCT registered among 13 of the largest centers of the TMRG network were analyzed. We report clinicopathological features, estimated 5-year event-free survival (5y-EFS) and 5-year overall survival (5y-OS) of MOGCT patients.

Results. We collected data from 147 patients including 101 (68.7%) FIGO stage I patients. Histology identifies 40 dysgerminomas, 52 immature teratomas, 32 yolk sac tumors, 2 choriocarcinomas and 21 mixed tumors. Surgery was performed in 140 (95.2%) patients and 106 (72.1%) received first line chemotherapy. Twenty-two stage I patients did not receive chemotherapy. Relapse occurred in 24 patients: 13 were exclusively treated with upfront surgery and 11 received surgery and chemotherapy. 5y-EFS was 82% and 5y-OS was 92.4%. Stage I patients who underwent surgery alone had an estimated 5y-EFS of 54.6% and patients receiving adjuvant chemotherapy 94.4% ($P < .001$). However, no impact on estimated 5y-OS was observed: 96.3% versus 97.8% respectively ($P = .62$). FIGO stage, complete primary surgery and post-operative alpha fetoprotein level significantly correlated with survival.

Conclusion. Adjuvant chemotherapy does not seem to improve survival in stage I patients. Active surveillance can be proposed for selected patients with a complete surgical staging.

1. Introduction

Malignant ovarian germ cell tumors (MOGCT) are rare ovarian neoplasms, accounting for 1% of all ovarian tumors. Worldwide incidence is about 0.37 per 100,000 women/year [1].Germ cell tumors affect mainly adolescents and young women and require specific treatments different from those of malignant epithelial ovarian tumors, with specific fertility sparing procedures. According to the World Health Organization (WHO), MOGCT are divided into different histological subtypes: dysgerminomas (accounting for 45%) and non-dysgerminomatous tumors (including immature teratomas, yolk sac tumors, embryonal carcinomas, choriocarcinomas and mixed germ cell tumors) [2].

International guidelines for treatment of women with MOGCT recommend in most cases fertility-sparing surgery followed by 3–4 cycles of bleomycin, etoposide, and cisplatin (BEP) adjuvant chemotherapy, even in early stages [1,3,4]. The current treatments result in at least 90% of overall survival (OS) in women with early stage MOGCT and to up to 80% of OS in patients with advanced disease [3,5]. Almost 60–70% patients with MOGCT are diagnosed at an early stage (stage I) and adjuvant chemotherapy for these patients remains debatable [6]. So far, no consensus was reached for these patients and more detailed paediatrics and adult's guidelines are still awaited. On the one hand, recommend adjuvant chemotherapy for all MOGCT reduces the risk of recurrence and results in improve EFS even for early stages. But, sparing adjuvant chemotherapy in patients at increased risk of relapse may subsequently correlate with an increased risk of mortality or fertility issues. On the other hand, systematic adjuvant chemotherapy may result in improper overtreatment and would not be appropriate. Indeed, surgery alone is often decided in young women to prevent late toxicities that must be considered as a major goal in patient care [1,7,8].

Randomized trials are scarce in the field of such rare tumors; the current practice is derived mainly from retrospective studies and assessment from male germ cell malignancies trials. Indeed, the establishment of a dedicated network to analyze collected data in patients with such rare tumors is fundamental.

The purpose of this study was to assess the outcome of patients registered in the French Rare Malignant Gynecological Tumors (TMRG) network; to identify prognostic factors likely to help appropriate risk-based decisions and finally to focus on stage I patients for whom the benefit of adjuvant chemotherapy and surveillance following surgery was explored.

2. Patients and methods

2.1. Data collection

The French network for Rare Malignant Gynecological Tumors (TMRG) established in 2011 and supported by the French National Cancer Institute (INCa) has been set up in order to improve management of these rare tumors with expert's opinion (histological diagnosis and multidisciplinary board decision for treatment). Its organization and functioning were previously described [9]. Each patient provides a written informed consent, data are anonymized and registered in a national database. Most of the cases are reviewed by an expert in anatomopathology and a multidisciplinary board determines for each patient the best therapeutic sequence. This multicenter retrospective analysis based on a prospective data collection was authorized by the French data protection authority (CNIL) in June 2018. The TMRG database was used to identify patients with ovarian germ cell tumor diagnosis. To note, non-ovarian germ cell tumors and mature teratoma with malignant transformation were excluded. Overall, 379 centers (including referent and non referent centers) collected data from 7302 patients with a rare ovarian tumor. Then, we carried on this case collection in the 13 largest centers among the 25 referent centers of the TMRG network in France.

2.2. Staging and tumor classification

Tumors stages were defined according to the International Federation of Gynecology and Obstetrics staging system for ovarian cancers (FIGO 2014) [10]. Histological type was defined according to the WHO classification [11].

2.3. Treatment and follow-up

In the case of early-stage disease (up Ic3 FIGO), guidelines recommended salpingo oophorectomy with peritoneal staging procedures (routine peritoneal cytology, multiple peritoneal biopsies, and omentectomy). In the case of advanced disease, a fertility-sparing approach is preferred whenever possible, especially in young women which consists on unilateral salpingo oophorectomy, omentectomy, and resection of macroscopic lesions on the peritoneum [3,4]. Chemotherapy used standardized international protocols for germ cells tumors: most of the patients were treated with a regimen combining cisplatin and etoposide (EP), or adding bleomycin to the latter regimen

(BEP). While requirement of adjuvant treatment was debatable in patients at early tumor stages, all patients at advanced stages received chemotherapy. Patient follow-up included clinical examination, blood marker measurements (alpha fetoprotein, HCG, LDH) and regular imaging closely during the first two years and at gradually increasing intervals thereafter for a mean time of 5 years, according to international recommendations.

2.4. Statistics

Survival rates were estimated using the Kaplan-Meier method. Overall survival was calculated as the time from the date of diagnosis to the time of last follow-up or death from any cause. Event-free survival (EFS) was calculated from the date of diagnosis to the date of first event, defined as relapse, progressive tumor or death from any cause. Univariate analysis using a log-rank test investigated potential correlations between survival and patient or disease covariates. No multivariate analysis was performed because of the reduced number of events in this cohort.

3. Results

3.1. Patient characteristics and treatment

We identified 262 patients with MOGCT in 13 referent cancer centers. Duplicates and non-exclusively germ cell tumors exclusion led to finally include 147 patients (Supplementary S1). Members of the pathological expert board in TMRG network reviewed 112 (76.2%) tumor samples. Patient characteristics are summarized in Table 1. Most of patients ($N = 101$, 69%) had a stage I disease at diagnosis. The median follow up was 51 [40–62] months. Survival follow up data were available for 137 (93.2%) patients including 94 (93%) out of the 101 patients at stage I·As expected, the 3 most represented histological entities were immature teratomas, dysgerminomas and yolk sac tumors (Supplementary S2). One hundred and forty (95%) patients underwent primary surgery (Table 1, Supplementary S3 and S4). Seventy-seven (75%) of the stage I patients had complete peritoneal staging (peritoneal washings, biopsies including omentectomy) and 94 had surgery with fertility preservation procedures. Sixteen patients underwent a retroperitoneal lymph node evaluation and 2 were positives. Sixty-six patients were at stage IA disease, 1 was at stage IB and 34 were at stage IC. Intraoperative surgical spill was documented in 11 cases (FIGO IC1). One hundred and six (72.1%) patients received chemotherapy (Table 1, Supplementary S3 and S4). Cisplatin-based chemotherapy has been administered to 106 patients and 98 patients received BEP/EP regimen. Adjuvant chemotherapy was administered to 28 of the 60 stage IA-B patients and to 31 of the 33 stage IC patients.

3.2. Outcome

Estimated 5-y OS and EFS rates were 92.4% (95%CI: 88%–96.8%) and 82% (95%CI: 75.8%–88.2%), respectively (Fig. 1). Twenty-four (15%) out of the 147 patients relapsed including 13 patients treated with surgery alone and 11 treated with adjuvant chemotherapy. All relapses occurred in the first 2 years. Overall, 8 out of the 147 patients died: 7 deaths occurred due to disease progression and 1 death due to chemotherapy toxicity. Three patients developed a contralateral tumor (one dysgerminoma, one teratoma and one yolk sac tumor). An assessment of toxicity was done retrospectively. We observed febrile neutropenia ($n = 16$), pulmonary toxicities ($n = 10$), neurotoxicities ($n = 8$), thromboembolism events ($n = 7$), cardiovascular dysfunctions ($n = 2$), gonadal dysfunctions (n = 8) and 2 second malignancies in our cohort.

Table 1
Patient Characteristics and treatment ($N = 147$).

	N
Median age (years)	25 [15–77]
Nulligravida	81 (55.1%)
Nulliparous	88 (59.9%)
Stage at presentation	
Ia/Ib	67 (45.6%)
Ic	34 (23.1%)
II	8 (5.4%)
III	27 (18.4%)
IV	9 (6.1%)
Unknown	2 (1.4%)
Histology	
Pure MOGCT	126 (85.7%)
Dysgerminoma	40 (27.2%)
Immature Teratoma	52 (35.4%)
Yolk Sac Tumor	32 (21.8%)
Choriocarcinoma	2 (1.4%)
Mixed MOGCT	21 (14.3%)
Surgery[a]	
Stage I	101
Complete peritoneal staging[b] (peritoneal washings, biopsies or omentectomie)	76 (75%)
Fertility-sparing Surgery	94 (94%)
Radical Surgery	7 (6%)
Stage II-IV	44
Fertility-sparing Surgery	32 (72.7%)
Radical Surgery	12 (27.3%)
Chemotherapy[c]	
Stage I	100
Adjuvant chemotherapy	62 (62%)
No adjuvant chemotherapy	38 (38%)
Stage II-IV	44 (100%)

[a] Missing data n = 2.
[b] Missing data n = 1.
[c] Missing data $n = 3$.

3.3. Early stage

In the stage I patient population, the 5y-EFS rates were respectively 94.4% in patients treated with adjuvant chemotherapy ($N = 59$) and 54.6% in patients who underwent surgery followed by surveillance ($N = 35$) ($P \langle 0{,}00001$) (Fig. 2A). The 5y-OS rates were similar with 96.3% and 97.8% respectively (*NS*) (Fig. 2B). In the 17 patients who relapsed, all but 1 underwent chemotherapy. In the 35 patients treated with surgery alone, 13 (37%) relapsed: 6/16 (37.5%) patients with pure dysgerminoma, 3/15 (20%) immature teratoma, 3/3 (100%) YST patients and one (100%) other mixed tumor. All relapsing patients were staged IA patients (Fig. 3). Median time to relapse was 11.5 (1–24) months. Eight of the 13 had previous adequate peritoneal staging. Eleven of them received chemotherapy at relapse (1 refused treatment and was lost to follow-up; 1 underwent salvage surgery without chemotherapy). Overall, 11/12 patients were successfully treated at relapse (one missing data). The remaining patient (immature teratoma) died from septic shock following grade 4 neutropenia after the first cycle of BEP chemotherapy.Among the 4 patients diagnosed at stage I who relapsed despite adjuvant chemotherapy, 3 had received BEP as

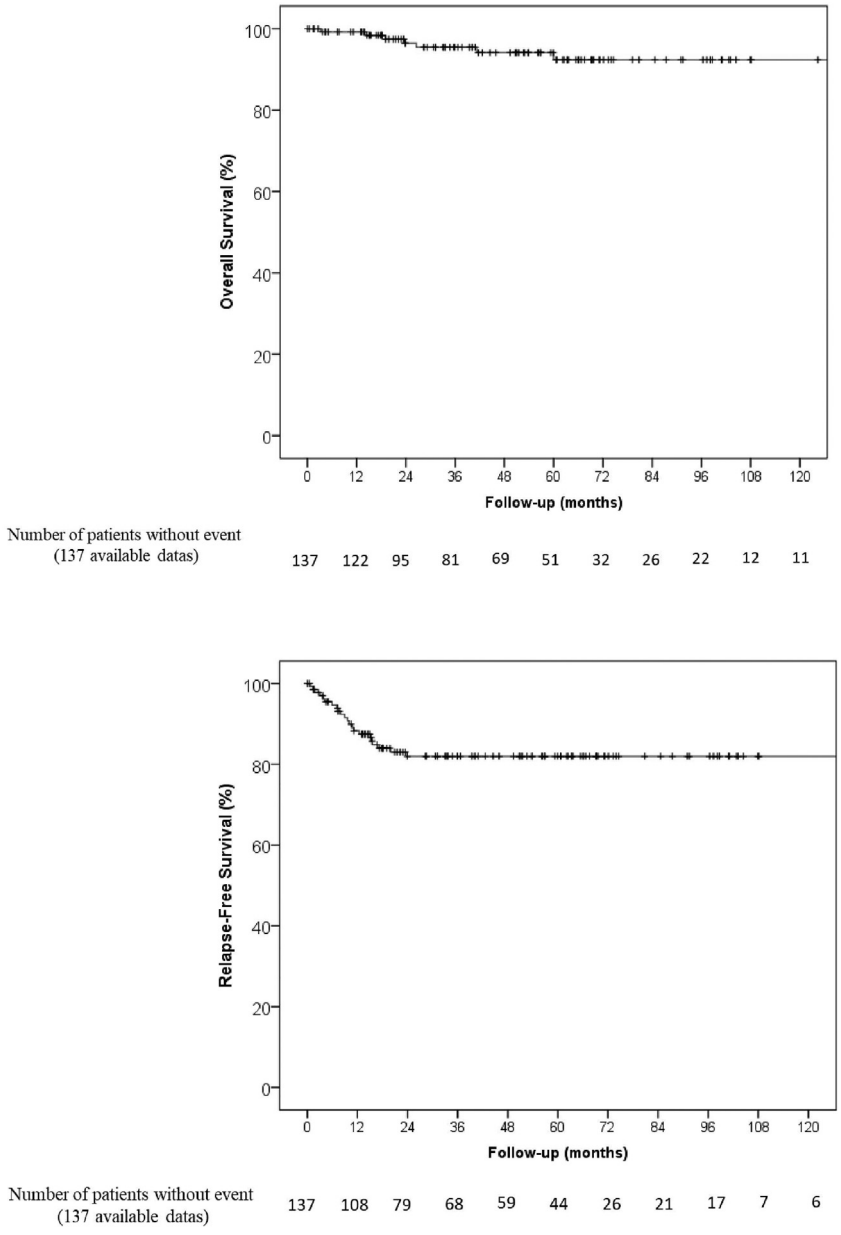

Fig. 1. Kaplan Meier Estimates of Overall Survival (A) and Event Free Survival (B).

adjuvant treatment. One patient with YST died from disease progression while the 3 remaining patients were alive following salvage treatment (2 patients received EP protocol and 1 received VeIP protocol).

3.4. Advanced stage

At advanced stages (FIGO II-IV), progressive disease or relapse was diagnosed in 7 patients (16%, Supplementary S5). Median time to relapse was 7.5 (1–15) months. All patients received salvage chemotherapy: VeIP ($N = 3$), BEP ($N = 2$), Epirubicin Docetaxel ($N = 1$) and Carboplatin Paclitaxel ($N = 1$). Two of them received high dose chemotherapy with autologous stem-cell support. Six patients died and one was salvaged with treatment (dysgerminoma, 4 BEP cycles).

3.5. Prognostic factors

The univariate analysis identified FIGO stage, complete surgery and post operative αFP as predictive factors of OS (Table 2). No differences were found using the covariates postoperative HCG, LDH level, YST subtype (trend to associate with at poorer prognosis, $P = .076$), or presence of lymphovascular space invasion (LVSI).

4. Discussion

This retrospective study is one of the largest cohort of MOGCT in adults. The major finding of our study is to show, that absence of adjuvant chemotherapy in stage I MOGCT patients has no impact on estimated 5 y-OS if patients receive chemotherapy at relapse. This result may help to carefully reconsider efficacy and toxicity balance in stage I MOGCT.

Overall, survival results showed an estimated 5-year OS of 92.4% and an estimated 5-year EFS of 82% all tumors combined. These results are consistent with OS and EFS reported in previous clinical trials [3,11–13]. Median time to relapse was 9 [1–24] months. Our serie shows that relapses occurred in the first 2 years following diagnosis as previously reported [15]. These data highlight that active surveillance

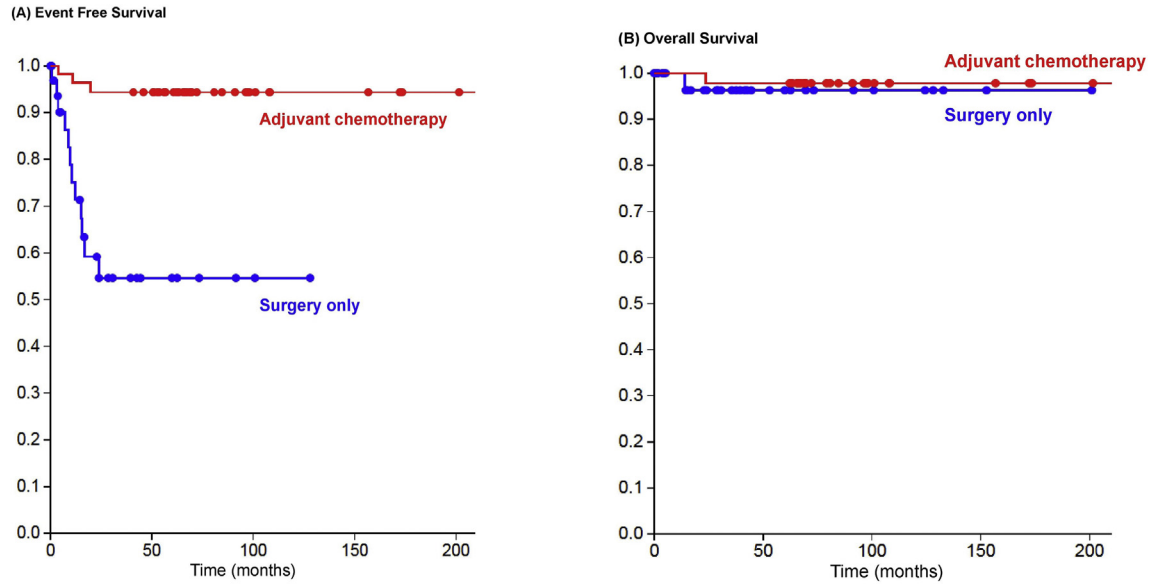

Fig. 2. Kaplan Meier Estimates of Event Free Survival (A) and Overall Survival (B) according to adjuvant CT or surveillance following initial surgery in stage I disease.

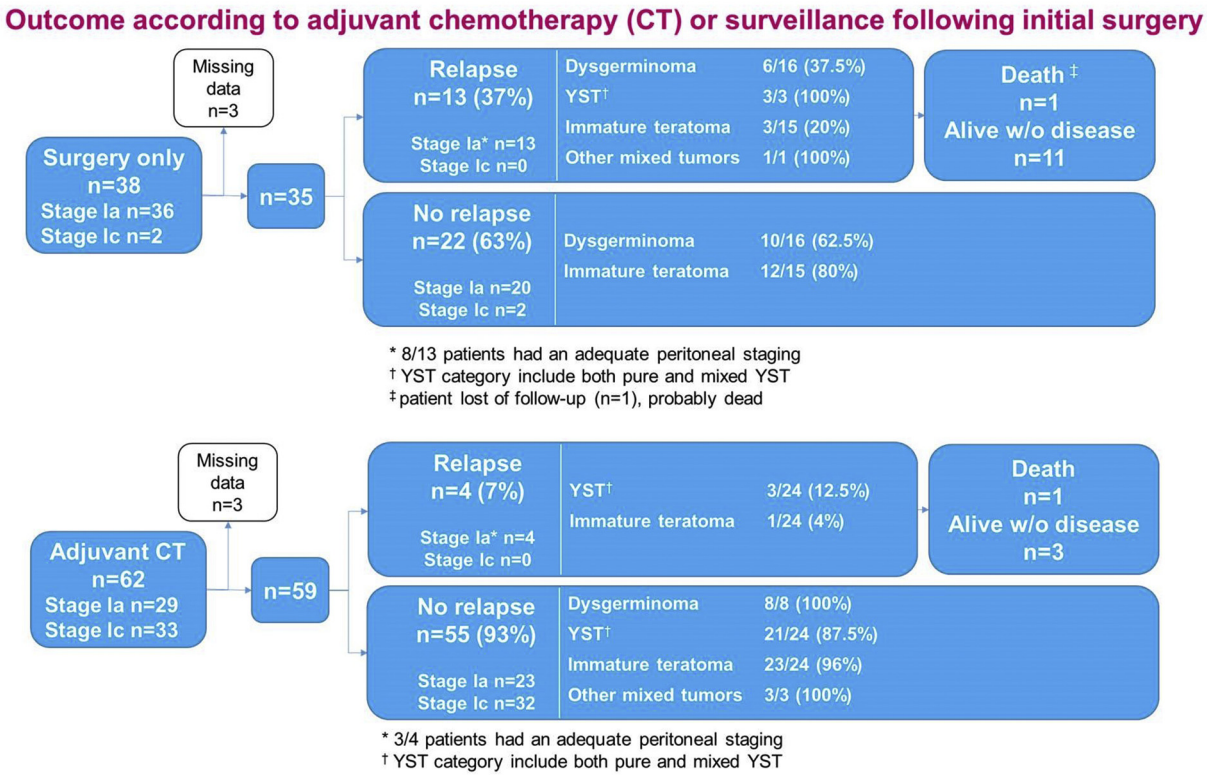

Fig. 3. Outcome according to adjuvant chemotherapy or surveillance following initial surgery for stage I MOGCT.

is crucial in the first 2 years. Both ESMO and NCCN have released guidelines about active surveillance [1,16]. ESMO recommends clinical examination and blood markers measurements monthly for the first year, 2 monthly for the second year, 3 monthly for the third year, 4 monthly for the forth year and 6 monthly from the fifth to the tenth year. Moreover, patients have to undergo CT chest abdomen and pelvis at 1, 3 and 12 months plus pelvic US and chest X-ray regularly until 10 years. Platinum-based chemotherapy regimen using BEP/EP or VIP/VeIP regimen has been offered in most patients [17,18]. Known chemotherapy-related toxicities occurred. Acute toxicities including neutropenia grade ≥ 3 (70%), febrile neutropenia (7%), thrombocytopenia grade ≥ 3 (8%), mucocutaneous toxicity (8%), neuropathy (25–30%), ototoxicity (20–25%), nephrotoxicity (3%) and pulmonary toxicity (9%) are the most common [19,20]. Late toxicities including cardiovascular disease/hypertension (6–10%), gonadal dysfunction and second malignancies (relative risk ~1.5–2.1) are much less common but can last a lifetime [21]. All these toxicities should be considered before recommending adjuvant treatment [1].

Table 2
Univariate analysis of 5-year OS ($N = 137$).[a]

Variable	No of patients[b]	OS % (sd)	*P*
Stage FIGO	137		
I	94	97.3%	*0.001*
II	8	100%	
III	26	85.6%	
IV	9	61%	
Lymphovascular invasion	125		
Yes	11	100%	*0.51*
No	114	80.6%	
Complete surgical resection	134		
Yes	114	85.1%	*0.002*
No	20	73.5%	
Postoperative AFP (ng/mL)	119		
≤7	65	97.1%	*0.048*
>7	54	86.8%	
Postoperative LDH	90		
Normal	78	92.2%	*0.402*
>Normal	12	88.9%	
Postoperative HCG	112		
Normal	111	93.7%	*0.8*
>3	1	100%	
YST histology	137		
No	92	85.6%	*0.076*
Yes	45	95.8%	
Choriocarcinoma histology	136		
No	134	81.4%	*0.002*
Yes	2	50%	

SD: standard deviation.
[a] Survival data is available for 137 patients only.
[b] Data is missing for lymphovascular invasion ($n = 12$), modality of surgery (n = 3), postoperative AFP ($n = 18$), LDH ($n = 47$) and HCG ($n = 25$), choriocarcinoma histology (n = 1).

Patients at advanced stages, all received chemotherapy. Six out of 7 relapsed patients died despite salvage treatments, highlighting their poor prognosis at relapse. While high dose chemotherapy with autologous stem-cell support may be proposed in relapsed patients [22], the small number of patients treated did not allow any conclusion. However, discussions on case-by-case basis should take place within the multidisciplinary tumor board. Treatment of refractory tumors remains unsatisfactory, and new approaches are needed to further improve outcomes. We believe that international collaboration should be established to thoroughly analyze the biological characteristics of these tumors.

For patients at early stages, the current questions are different and essentially concern the need for therapeutic de-escalation. Indeed, preventing and minimizing short-term and long-term toxicity related to chemotherapy regimen is of major concern for these young patients, for whom surgery alone is likely to be curative in most cases. However, international recommendations still mention the necessity of adjuvant treatment consisting in 3–4 cycles of BEP chemotherapy after surgery. Our study showed that 38 (37.6%) of the patients at early stage did not receive chemotherapy and 13 (34%) patients relapsed. Despite a significant difference on estimated 5 y-EFS, we show that absence of adjuvant chemotherapy in stage I MOGCT patients has no impact on estimated 5 y-OS if patients receive chemotherapy at relapse. This result is consistent with other recent studies suggesting excellent survival outcome in stage I patients spared from adjuvant chemotherapy [7,20–22].

Moreover, some factors are critical to determine the risk of relapse in early stages especially pathologic subtype. In this study, most patients without recurrence following surgery alone who did not receive adjuvant chemotherapy were diagnosed with a dysgerminoma or immature teratoma tumor, whereas all patients suffering from a yolk sac tumor histology component relapsed. We believe that our data confirm that systematic adjuvant chemotherapy should be applied in all stage I yolk sac tumors patients as it has been already recommended [23,25,26,27]. We showed that sparing stage Ia-Ib grade 1 immature teratoma and some dysgerminoma patients from adjuvant chemotherapy may be a valid option following adequate surgical staging, complete resection and normal post-operative serum marker levels. Of note, ESGO and ESMO recently published recommendations for MOGCT treatment in which surveillance is proposed for selected stage I tumors. Our serie shows a higher relapse rate for dysgerminomas than that observed in the Italian series. This discrepancy may result from the relatively small numbers of patients in both series. Therefore, as proposed for testicular seminomas with a cure rate above 95% [28,29], one course of carboplatin AUC7 for dysgerminomas should be investigated. Similarly, in patients with stage I non seminomatous testicular cancer, 1–2 adjuvant BEP cycles are appropriate to cure mainly all patients [30]. We assume this treatment for non dysgerminomatous MOGCT patients should be further explored. Nevertheless, this therapeutic de-escalation requires careful assessment before being adopted routinely. Another important point remains the necessity of optimal staging peritoneal procedures. Indeed, the omission of appropriate staging peritoneal procedures seems to increase the recurrence rate, as a result of underestimation of advanced stage [1]. Active surveillance should be considered in confirmed stage I patients and peritoneal staging turns out to be essential to guarantee adequate management.

This study presents several limitations, we performed a retrospective analysis and faced with missing data especially related to preoperative markers; due to the rarity of these tumors and their general good prognosis, only univariate analysis was performed. A larger international cohort with more patients and more events is needed to build a valid prognostic score as proposed in patients with testicular germ cell tumors [31] or as suggested by Meisel and colleagues in patients with MOGCT [32].

5. Conclusion

Adjuvant chemotherapy should not be systematically proposed for stage I patients with exception for YST. Active surveillance is an acceptable alternative. A close follow-up during the first 2 years is essential. Further investigation is required to determine the optimal management of patients with MOGCT at advanced stages and relapsed disease. Prospective trials conducted through international collaborations like the Rare Cancers Europe Initiative are needed to develop risk-based treatment strategies for these rare tumors.

Disclosures

The authors reported no conflict of interest for this article.

Acknowledgments

Thanks to the French National TMRG (Tumeurs Malignes Rares Gynecologiques) Network and ARCAGY-GINECO group. We also would like to give special thanks to the clinical research associates, medical oncologists and medical interns who actively contributed to data collection/management. We equally wish to thank Nuchanard Chen, Amandine Charreton, Sophie Darnis and all clinicians and pathologists of the TMRG network for their work and implication within this network which is essential as it contributes to promote research studies like the present one, in the field of rare gynecological cancers: **Referent Clinicians of the TMRG network national and regional expert centers**: Eric Pujade Lauraine, Philippe Morice, Cyril Abdeddaim, Roman Rouzier; **Referent Pathologists of the TMRG network expert centers**: Mojgan Devouassoux, Sabrina Croce, Corinne Jeanne, Frédérique Penault-Llorca, Laurent Arnould, Anne-Sophie Lemaire, Emmanuelle Charafe-Jauffret, Cristina Leaha, Emmanuelle Guinaudeau, Olivier Renaud, Sébastien Henno, Gerlinde Averous, Eliane Mery-Lamarche, Agnès Leroux, Catherine Genestie, all members of the PathGyn group among which are Marie Aude Le Frere Belda and Pierre Alexandre Just.

Finally, we would like to thank all of the patients who have accepted to be registered on the TMRG network, thus allowing research studies in order to better treat, diagnose and establish the prognosis of patients with rare gynecological tumors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.06.491.

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