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# Fertility sparing surgery for patients with malignant ovarian germ cell tumors: 10 years of clinical experience from a tertiary referral center

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**Abstract**

**Purpose:** To describe a case series of patients with malignant ovarian germ cell tumors (MOGCT) treated exclusively with fertility-sparing surgery (FSS) with or without adjuvant chemotherapy.

**Methods:** We retrospectively reviewed the records of 27 patients with MOGCT treated in the Department of Obstetrics and Gynecology, University Hospital Center Zagreb, Croatia, between January 2009 and July 2019.

**Results:** The median age at diagnosis was 22 years, and the main symptom was abdominal distension (57.0%). The most prevalent histological subtype was immature teratoma (n = 13, 48.1%). Twenty-three patients (85.2%) had laparotomy and 4 (14.8%) had laparoscopy, without conversions. Lymphadenectomy was performed in 16 (59.3%) patients, with 184 removed lymph nodes, and omentectomy was performed in 19 (70.4%) patients. The rate of chemotherapy administration was 81.5%. The follow-up length ranged between 6.30 and 115.1 months (median: 49.60 months). No patient experienced tumor recurrence. The rate of complete gross resection was 100%. At the time of analysis, all patients were alive and disease free. Fifty percent of patients who actively tried to conceive after FSS became pregnant, with 12 deliveries.

**Conclusion:** This study suggests that FSS is a safe treatment option for MOGCT regardless of tumor stage and histological type.

**Keywords**: malignant ovarian germ cell tumors; fertility-sparing surgery; reproductive outcome; adjuvant chemotherapy.

## Introduction

Malignant ovarian germ cell tumors (MOGCTs) constitute approximately 2% to 3% of all ovarian malignancies, with an estimated incidence of 0.4 per 100,000 women [1,2]. MOGCT is typically encountered in late adolescence or young adulthood [2]. The most common types of MOGCTs are, in order of frequency, dysgerminomas (DG), immature teratomas (IT), yolk sac tumors (YST) and mixed germ cell tumors (mGCT). Other less common MOGCTs are embryonal carcinomas (EC), choriocarcinomas, and malignant struma ovarii tumors [3].
The use of cisplatin-based chemotherapy, introduced in the late 1970s for testicular cancer treatment, dramatically improved the overall and progression-free survival in patients with MOGCTs [4]. Furthermore, advances in surgical approaches made this malignancy curable, with high rates of fertility preservation [5]. Nowadays, fertility-sparing surgery (FSS) with or without adjuvant chemotherapy is widely accepted due to the high treatment success in early stage disease and may, after appropriate discussion and obtained consent, be applied in young women with advanced-stage MOGCTs who desire pregnancy [6]. The currently available results, generally based on case series, show excellent survival outcomes of FSS, with up to 93.3% pregnancy rate [1,5-8]. However, some aspects of FSS are still subject to considerable debate – for example, there is a lack of consensus regarding the role of omentectomy and lymphadenectomy during CSS [9-12].
A relatively low incidence of this heterogeneous group of tumors explains the paucity of evidence about the clinical behaviour, oncology and reproductive outcomes after fertility-sparing surgical management. The aim of the present study is to describe a series of MOGCT cases managed exclusively with FSS and with or without adjuvant chemotherapy in a single tertiary care institution.

## Patients and Methods

This retrospective, observational, single-center study, undertaken at the Department of Gynecology Oncology, University Hospital Center Zagreb, Croatia analyzed the data of all women diagnosed with MOGCT between January 2009 and July 2019. We included all patients treated with FSS due to their desire to preserve fertility regardless of tumor stage. The study was approved by the local ethics committee, and the requirement to obtain informed consent was waived. Demographic characteristics and data on signs and symptoms, comorbidities, gestational and parturition history before diagnosis, serum tumor markers, imaging examination, details of treatment, follow-up length, recurrence, reproductive outcomes after FSS, signs and symptoms of premature menopause and overall survival were collected from electronic medical records and hospital-based cancer registry. Information on histopathological subtypes, the degree of differentiation, tumor dimension, and mitotic rate was obtained from pathology reports. Tumor stage was determined according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 classification [13]. The patients staged before 2014 were restaged according to the 2014 FIGO criteria.

The choice of surgical approach mostly depended on preoperative physical and imaging findings. If the tumor diameter was greater than 10 cm and preoperative imaging showed enlarged lymph nodes and omentum involvement, laparotomy was performed.

In our patients, FSS management consisted of preserving the uterus and at least part of the contralateral ovary; either comprehensive surgical staging (CSS) or unilateral salpingoophorectomy (USO) were performed. CSS was performed by highly skilled and experienced gynecologic oncology surgeons after a proper preoperative assessment, and USO was performed by gynecological surgery specialists. CSS included ipsilateral adnexectomy, omentectomy, pelvic +/- para-aortic lymphadenectomy, appendectomy, multiple biopsies and peritoneal cytology. USO included ipsilateral adnexectomy, intraoperative exploration including excision of all visible lesions, multiple peritoneal biopsy and peritoneal cytology. We performed CSS based on preoperative imaging assessment and intraoperative findings. In some instances, for apparent early-stage patients with lesions confined to the ovary, we made peritoneal fluid cytology, and if positive, we also performed CSS.

Adjuvant treatment options were discussed by a multidisciplinary tumor board. Adjuvant chemotherapy was administered after surgical treatment and confirmed staging.

All patients were followed up periodically in the outpatient department. The follow-up included clinical, serum tumor marker and imaging assessment. The follow-up length was calculated from the date of the first surgery until the date of the last medical record.

Descriptive statistics were used to describe the sample. Categorical variables are expressed as counts and proportions, and continuous variables as median and range. The analysis was performed with Statistica software package, version 13.2., Dell Inc., USA, 29 2015.

**Results**

Between January 2009 and July 2019, we identified 27 patients with MOGCT who underwent FSS management. In the same period, 721 primary surgical procedures for all types of ovarian cancer were performed in our department, yielding a MOGCT incidence rate of 3.7% per year. The median age at diagnosis was 22 years (range: 17-41). At the time of diagnosis all patients, except one, were younger than 30 years. Twenty-one patients (77.8%) were nulliparous. The main MOGCT symptom was abdominal distension (57.0%), followed by abdominal pain (49.6%). Six (22.2%) patients had a family history of gynecological cancer. The most prevalent histological subtypes were IT (n = 13, 48.1%) and DG (n = 7, 26.0%). In the IT group, the most common grade was grade 2, which accounted for 46.2% of the observed ITs (Table 1). The most prevalent disease stage was Stage I (n = 19, 70.4%). Stage II/III disease was present in only 8 patients (29.6%) (Table 2). Gliomatosis peritonei occurred in 30.8% (4 out of 13) ITs.

All patients underwent preoperative imaging assessment, including tumor lesion quantification. The median tumor size was 15.50 cm (range: 8-30 cm).

Table 1 shows the number of patients with each histopathological type who had elevated tumor markers. It is important to note that 75% patients had available preoperative data on all tumor markers. Preoperative serum lactate dehydrogenase (LDH) (> 241 U/L) was elevated in 6 out of 6 patients (100.0%) with dysgerminoma, and preoperative alpha-fetoprotein (AFP) (> 13 ng/mL) was elevated in 15 out of 19 (78.9%) nondysgerminomatous patients. Human chorionic gonadotropin (β-hCG) was elevated (> 4 IU/L) in 4 out of 9 patients (44.4%) with MOGCT. Preoperative cancer antigen 125 (CA – 125) was elevated ( > 23 U/mL) in 17 out of 24 patients (70.8%).

A total of 16 patients (59.3%) underwent CSS, while 11 patients (40.7%) underwent USO. The surgical approach was laparotomic in 23 (85.2%) patients, and laparoscopic in 4 (14.8%) patients, without conversions. Lymphadenectomy was performed in 16 (59.3%) patients and omentectomy was performed in 19 (70.4%) patients. The 3 additional omentectomies were performed in the USO group due to extensive tumor adhesions to the omentum.

Ascites was present in 13 (48.1%) patients, while 8 patients (29.6%) had positive cytology. There were no pregnancies at the time of diagnosis.

The first-line chemotherapy regimen was BEP (bleomycin, etoposide and cisplatin), except for stage IA grade 1 IT, stage IA DG and IB DG patients. Based on the decision of the multidisciplinary tumor board, IB DG patients did not receive adjuvant treatment because they underwent CSS (including para-aortic lymphadenectomy) (Table 2).

Non-BEP protocols included TP (paclitaxel and cisplatin) and VAC (vincristine, dactinomycin and cyclophosphamide) regimens for EC and IT treatment (stage IIIA1, grade 3), respectively. The rate of chemotherapy administration was 81.5%. A total of 74.1% of patients received BEP regimen (Table 2). None of our patients received neoadjuvant chemotherapy.

Follow-up data and data on the conception after FSS were available for all 27 patients (Table 2). The follow-up length ranged between 6.30 and 115.1 months, with a median of 49.60 months. No patients experienced tumor recurrence and all patients achieved complete gross resection. At the time of analysis, all patients were alive and disease free.

After the end of treatment, 20 patients (74.07%), all of them younger than 30 years, actively tried to conceive. Ten of these patients (50.0% overall, 6 with IT, 2 with DG and 2 with YST), who underwent either CSS or USO, became pregnant. There were 12 deliveries, 9 of which occurred after 37 completed weeks of gestation. The pregnancy rate was equal in the CSS and USO group (50.0%) (Table 2).

All women in our group were premenopausal, 92.6% of patients reported return of menstrual function within 12 months of completing adjuvant chemotherapy, while 2 patients (7.4%) suffered from premature menopause as a consequence of treatment.

**Discussion**

The present study showed that FSS in MOGCT patients did not compromise the recurrence, progression-free and overall survival rates. Such findings are particularly important in adolescents and young, nulliparous women or women of reproductive age who wish to preserve fertility.

MOGCT incidence in our study was 3.7%. A slight increase compared with other literature findings can be explained by the fact that our Clinic is the only tertiary center in Croatia that systematically manages this type of ovarian tumor [1]. However, this rate also reflects the rarity of this tumor, with approximately 3 cases per year in our center.

There is an increasing trend of MOGCTs in young women [2,3]. The median age (22 years) at the time of diagnosis indicates that MOGCT patients are often at an age when fertility preservation and overall survival are important concerns.

Guidelines for the treatment of epithelial ovarian cancer recommend the use of CSS in the treatment of MOGCT. Recent reports support the use of FSS in patients with MOGCT, regardless of tumor stage and even of disease recurrence [1,6,14-19].

CSS is now routinely applied for MOGCT treatment, but its efficacy and safety is still under debate [9,12]. Compared with USO, CSS causes greater intraoperative blood loss and has higher complication rate, which can delay the administration of adjuvant chemotherapy. Furthermore, due to the complexity of the procedure, CSS should be performed by a gynecologic oncologist.

Yang et al. [5] showed in 2015 that the fertility-preserving group had 15.3% lower mortality rate than the non-fertility-preserving group ($p = 0.054$) but a similar 5-year progression-free survival (PFS) rate.

Weinberg et al. confirmed the excellent overall survival in patients with MOGCT treated with FSS followed by chemotherapy when appropriate. The overall survival was 100% despite the fact that 47.5% of the patients had a disease that spread beyond the ovaries at the time of diagnosis [20]. A retrospective study by Liu et al. on 92 patients with MOGCTs found that the USO group had slightly increased overall 5-year survival rates and 5-year tumor-free survival rates compared with the CSS group (97% and 97% vs. 92% and 87%, respectively) but the difference was not significant [19]. Moreover, the USO group had significantly shorter operation time ($p < 0.001$), significantly lesser intraoperative blood loss ($p = 0.004$) and significantly lower complication rate ($p = 0.003$) [19]. These findings indicate that USO can be used as a treatment of choice for MOGCT in disease stage I/II.

Moreover, Park et al., in 28 patients with stage III and IV, showed that FSS approach can be performed even in advanced stages of MOGCT [6].

In our study, 16 patients (59.3%) received CSS treatment and 11 (40.7%) received USO treatment. At the end of the analysis, all patients were alive, with 100% overall survival and no differences in the survival rate between the CSS and USO group. Our results are similar to those of previous studies [19,20].

Due to tumor biological behavior, most of the MOGCT patients seek medical care at an early disease stage [17]. However, in our study 29.6% of patients presented to our Department at an advanced stage of disease, a rate similar to those reported in other studies [17,21].

Independent prognostic factors for recurrence and overall survival were postoperative residual

tumor size and incomplete peritoneal surgical staging [6,17,18,22], which was also the case in patients with recurrent MOGCT who underwent salvage surgery [23,24]. Karalok et al. achieved maximum cytoreduction in 58% of patients. These patients had a 5-year disease-free survival (DFS) rate of 93%, compared with 29% in the suboptimal cytoreduction group. Furthermore, in the suboptimal cytoreduction group only 32% of the patients survived, compared with no deaths in patients with complete gross resection (p=0.001) [17]. In addition to low incidence of this tumor group [2,3], reports concerning prognostic indicators are scarce.

Lymph node metastases are a poor prognostic indicator, with a prevalence of 18% among all subtypes of MOGCTs [10,25]. Patients with DGs are at greatest risk of metastatic adenopathy (almost 30%) [25]. Mahdi et al. found relatively low lymph node metastasis rates for IT and DG, 1.4% and 11.3%, respectively [10], while Qin et al. reported the rate of 0.8% (1 out of 119 patients) in early stages of MOGCT [9]. According to Mahdi et al, neither retroperitoneal excision nor lymph node metastases were independent prognostic factors for early stages of MOGCT [10].

We performed lymphadenectomy in 16 patients (11 pelvic and 5 pelvic + para-aortic), mainly in patients with enlarged lymph nodes. Only 3 patients (18.7%) had lymph node metastases, which did not compromise the recurrence rate and overall survival. In order to reduce the overall morbidity and improve the patients' quality of life and reproductive outcome, lymphadenectomy should be considered owing to the reported low metastatic rates in this tumor group [1].

CSS traditionally includes omentectomy. In early-stage epithelial ovarian cancer, metastatic omental disease affects up to 7% of patients with macroscopically normal omentum [12]. Xu et al. showed no significant difference in 10-year overall survival between patients with and without omentectomy at stage I and II disease [12]. We performed omentectomy in 19 (70.4%) patients and found no metastatic disease. Our results suggest that omentectomy can be omitted in the early stage of MOGCT. However, there is an evident lack of consistent data regarding the usefulness of omentectomy in this particular patient group.

CSS followed by platinum-based chemotherapy is the cornerstone treatment for MOGCTs, except for stage IA DG and IA grade 1 IT, where surveillance only is recommended [26]. The issue on whether other stage IA and IB MOGCT patients should receive adjuvant chemotherapy is still controversial. Several studies questioned the role of adjuvant chemotherapy in early-stage MOGCTs [18,27-29].

The MITO-9 study reported the safety of surveillance approach. In their study, the relapse rate among 44 patients in the surveillance group was 20.5%, with unaffected overall survival [18]. Of note, 26% of relapsed patients had not received complete peritoneal surgical staging [18]. Patterson et al [27] adopted a close surveillance program after surgery for all stage IA MOGCTs. They enrolled 37 patients (median age 26) in a 22-year period, with a median follow-up of 6 years. The relapse rates for stage IA nondysgerminomatous tumors and dysgerminomas were 36% and 22%, respectively. Only 1 of these patients could not be salvaged. They recommended surveillance for all stage IA MOGCTs, and regardless of grade in the cases of IT.

There is a need for more studies addressing the safety of surveillance in patients with IT grade tumors. Pashankar et al. reported 20% recurrence rate in IT G3 despite adjuvant chemotherapy [30]. Vicus et al reported that two thirds of stage I G2 or G3 IT patients who had a recurrence were chemoresistant and died of their disease [31]. The question is whether such patients would have a better prognosis if they received adjuvant chemotherapy instantly or they inherently had a poor prognosis.

In our study, all patients, except stage IA grade 1 IT, stage IA DG and IB DG, received adjuvant chemotherapy, so we cannot conclude on the surveillance policy efficacy. Chemotherapy was generally tolerated well, with no bleomycin-related pulmonary toxicity and secondary leukemia. The recurrence rate at the end of analysis was still 0%, even in DG IB patients, showing the effectiveness of adjuvant BEP regimen in properly selected and surgically staged patients. However, the histopathologic heterogeneity (especially in stage I ITs) makes it difficult to conclude on the usefulness of the surveillance approach.

In their retrospective, multicenter study, Tamauchi et al identified 105 patients with MOGCT who received FSS in a median follow-up period of 10.4 years [1]. In their study, the pregnancy rate among patients who attempted to become pregnant was 93.3% and the rate of term deliveries was 96.4%. The study's main aim was to gather data on reproductive outcomes in survivors, since there is usually a gap of at least 5 years between the age at diagnosis and pregnancy age. Likewise, our median follow-up period (49.60 months) could be viewed as a limitation of the reproductive outcomes assessment. In our study, 20% of patients with FIGO stage II and III MOGCT had a successful delivery, which is a rate identical to that from a large recently published report by Tamauchi and associates [1]. Additionally, Tamauchi et al. concluded that advanced tumor stage and even disease recurrence should not guide the decision to avoid FSS [1]. The pregnancy rate in several studies including FSS + adjuvant chemotherapy approach ranged from 13.3% to 45.9% [19,29,32,33]. Our study

reported the 50% pregnancy rate with 9 term deliveries. These results suggest a sufficient potential for pregnancy in these patients, unaffected by CSS and chemotherapy, and are in accordance with other studies [14,19,20].

The effect of platinum-containing chemotherapy on menstrual function has been studied in several case series. Weinberg et al. found 100% rate of return of menstrual function within 12 months of completing adjuvant chemotherapy [20]. In the study by Low et al., the rate was 91.5% among 47 patients with MOGCT [8] and in the study by Gershenson it was 87% after surgery and cisplatin-based chemotherapy [14]. In our study, this rate was 92.6%. Our results confirm that chemotherapy used for MOGCT does not affect fertility potential.

The current study is limited by a small sample size and retrospective design, which is prone to bias in data collection. However, our results are derived from a single institution, a referral center for cancer treatment in Croatia with negligible differences in the details of surgery and chemotherapy administration. Other strengths of our study are a relatively long median follow-up and specific evaluation of FSS outcomes.

In conclusion, this study suggests that FSS is a safe treatment option for MOGCT regardless of tumor stage and histological type. Furthermore, our results indicate that the chemotherapy used for MOGCTs does not affect patients' reproductive capability.

## Compliance with ethical standards

## Ethical approval and informed consent

On July 15th, 2019., the study was approved by the Institutional Review Board of the University Hospital Center Zagreb, Croatia (serial IRB number: 0097/2019).

## Conflict of interest

The authors have no conflicts of interests to declare in relation to this article.

## Informed consent

Due to the retrospective design of the study, the informed consent to participate is not applicable.

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