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ORIGINAL ARTICLE

Survival and reproductive outcomes after fertility-sparing surgery and postoperative adjuvant chemotherapy in malignant ovarian germ cell tumors

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ABSTRACT

Objective. Ovarian germ cell tumors are uncommon tumors with an excellent prognosis. Our aim in this study is to retrospectively examine the reproductive and survival results of ovarian malignant germ cell tumors (OMGCTs) following fertility-preserving surgical intervention and postoperative chemotherapy.

Patients and Methods. Demographic, clinical and outcome data of twenty-two OMGCT patients managed during the period from January 2012 to December 2016 were gathered and analyzed.

Results. The patients' median age was 25 years at the time of diagnosis. Dysgerminoma represented 40.9% of cases and ten patients had stage I disease. Unilateral salpingo-oophorectomy with preservation of the contra-lateral ovary and the uterus was the standard surgical procedure. The median number of chemotherapy courses was three courses. The median follow-up was 48 months. The overall five-year survival rate was 100%, while the disease-free five-year survival rate was 90%. Thirteen patients (59%) reported regular menstrual cycles. Fifteen patients (68.2%) wished to conceive, 10 (66.7%) became pregnant naturally and 8 (53.3%) gave birth to living children.

Conclusions. Survival and reproductive results following fertility-preserving surgery and adjuvant chemotherapy in OMGCTs are satisfactory, although counseling and education are still required.

Key words

Ovarian malignant germ cell tumor; treatment; outcomes.

List of abbreviations

AFP: Alpha fetoprotein.

AJCC: American Joint Committee on Cancer.

BEP: Bleomycin, Etoposide, and Cisplatin.

DFS: Disease-free survival.

EMA-CO: Etoposide, methotrexate, dactinomycin - cyclophosphamide,vincristine.

EP: Etoposide, platinum.

ERK: Extracellular signal-regulated kinase

FIGO: The International Federation of Gynecology and Obstetrics.

HCG: Human chorionic gonadotrophin.

LDH: Lactate dehydrogenase.

MEK: Mitogen-activated protein kinase

NCCN: National Comprehensive Cancer Network

OMGCT: Ovarian malignant germ cell tumors.

OS: Overall survival.

RAF: Rapidly accelerated fibrosarcoma

RAS: Rat sarcoma

TNM: Tumor-node-metastasis.

USO: Unilateral salpingo-oophorectomy.

WHO: World Health Organization.

Introduction

Ovarian malignant germ cell tumors (OMGCTs) represent approximately 5% of all ovarian malignancies and are mostly diagnosed in young female patients[1]. OMGCTs develop from primordial germ cells and include several subtypes e.g. dysgerminoma, yolk sac tumor (also referred to as endodermal sinus tumor), immature teratoma, non-gestational choriocarcinoma and embryonal carcinoma)[2].

Most OMGCTs cases are diagnosed at an early stage[3]. According to American National Comprehensive Cancer Network (NCCN) 2017 guideline for ovarian cancer, the standard treatment regimen for OMGCT with fertility desiring is fertility-preserving surgery (which involves conservation of

the contra-lateral ovary and the uterus either with or without comprehensive staging). Because of their exquisite chemo-sensitivity, fertility-preserving surgery can be achieved in the majority of cases with a cure rate of >95%[4].

The adjuvant platinum-based chemotherapy protocols have been the therapy of choice and the BEP (bleomycin, etoposide, and cisplatin) regimen is the one that is most frequently administered after surgery[5][6].However, the effectiveness of such therapy in terms of pregnancy rate and live birth outcomes is not well known.

We conducted this retrospective research to describe the clinico-pathological characteristics and examine the survival and reproductive results of OMGCT patients following fertility-preserving surgical intervention and postoperative adjuvant chemotherapy at our hospital.

Patients and Methods

Retrospective analysis was done on twenty-two OMGCT patients who underwent fertility-preserving surgical intervention and postoperative adjuvant chemotherapy from January 2012 to December 2016 at Kasr Al-Aini Hospital - Faculty of Medicine - Cairo University (Department of Obstetrics & Gynaecology and Centre of Clinical Oncology and Nuclear Medicine). Inclusion criteria were: all patients were younger than 35 at the time of their initial treatment, pathologically proven malignant ovarian germ cell tumors after fertility-sparing surgery, and complete follow-up data. Exclusion criteria were as follows; patients with benign ovarian germ cell tumors, double primary cancers, severe comorbidities that preclude administration of chemotherapy, and patients who lost follow-up or denied access to their medical records for research purposes.

Abdominal discomfort/pain, pelvic mass and arising of tumor markers such as human chorionic gonadotrophin (HCG), alpha fetoprotein (AFP), or lactate dehydrogenase (LDH) lead to the OMGCT diagnosis which is confirmed by histopathological examination after surgical intervention. Expert gynaecological pathologists at our institution verified the pathological diagnosis in accordance with the 2014 classification of female reproductive organ tumors by the World Health Organization (WHO). The International Federation of Gynecology and Obstetrics (FIGO) staging system for germ cell tumors (7th ed., 2010) and the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification were used to stage the tumors[7].

The collected data covered the demographics of the participants, clinical and pathological features, management and survival outcome. Reproductive results, including the rate of pregnancy and live birth rates, were conducted. Hospital medical records and interviews via telephone were used to gather the update information until December 31, 2021. The ClinicalTrials.gov registration number for this study is NCT05905289 and the Cairo University Research Ethics Committee approved it (N-181-2023).

Regardless of the tumor's stage, OMGCT patients who want to preserve their fertility can get treatment with fertility-sparing surgery. The term "fertility preservation operation" refers to preserving the uterus and the contra-lateral ovary either accompanied by or without complete surgical staging (lymphadenectomy with omentectomy) by an exploratory laparotomy. Comprehensive surgical staging was skipped for teenage patients who were in the early stages. Postoperative chemotherapy was conducted based on histopathology, grade and stage. Chemotherapy was given to all patients, but with different plans and regimens.

Statistical analysis

The information was entered and coded using IBM SPSS software version 23 (Armonk, NY: IBM Corp.). Sets of nominal or category variables were compared utilizing the Chi-square/Fisher exact test. Categorical variables were represented by numbers and percentages. Research on survival was done with the Kaplan-Meier method. The two survival curves were compared using the log-rank test. When a p-value was less than 0.05, it was considered statistically significant. The number of months from the time of diagnosis to the time of death was used to calculate overall survival (OS), while the number of months from the date of full remission (after surgery and/or chemotherapy) to the date of death or recurrence was used to calculate disease-free survival (DFS).

Results

In the period from 2012 to 2016, 27 patients underwent fertility-preserving surgery and postoperative chemotherapy at Kasr El-Aini Hospital. 22 of them had completed follow-up information.

Patients' characteristics:

With a range of 14 to 32 years, the patients' median age was 25. Pelviabdominal swelling and localized pain were documented in 45.4% and 50% respectively. Dysgerminoma was the leading pathology (40.9%).The pathological and clinical characteristics of the study's patients are listed in Table 1.

Nine patients underwent fertility-preserving surgery with full staging (omentectomy with pelvic lymphadenectomy). In other cases, a unilateral salpingo-oophorectomy (USO) was performed. The rule was complete surgical resection (R0). In the current study, no serious complications were noted. BEP treatment was administered to twenty patients. The two remaining patients received EMA-CO (Etoposide, methotrexate, dactinomycin - cyclophosphamide, vincristine) and EP (Etoposide, platinum). The number of chemotherapy sessions ranged from one to five sessions, with a median of three sessions.

Overall Survival (OS):

With a median of 48 months, the follow-up period varied from 24 to 84 months. Patients are all living at the most recent check-up. The OS median was not attained. The five-year Overall Survival was 100 percent.

Disease-free survival (DFS):

The comparison of DFS failed to yield significant data because of the small number of treatment failures in only two patients. The median DFS was not achieved. The 5-year DFS rate was 90 percent (Figure 1).

Reproductive outcome:

Thirteen patients (59%) reported regular menstrual cycles, while other patients claimed to have minimal menstrual flow or shorter menstrual cycle length. Neither the patients' age (OR:1.09, 95%CI:0.92-1.28, p=0.288), clinical stage (OR:1.07, 95%CI:0.19-5.91, p=0.937), nor the number of chemotherapy sessions (OR:1.65, 95%CI:0.70-3.92, p= 0.25), had any impact on the patients' menstrual status.

15 of the 22 patients (68.2%) desired to become pregnant. The remaining patients were either single or unwilling to conceive. Ten out of 15 patients (66.7%) became pregnant after finishing chemotherapy, with a mean interval of 16.5 ±11.7 months, ranged from 7 to 40 months. Eight patients gave birth to living children free of serious birth abnormalities apart from one with congenital heart anomalies. There were two miscarriages. All of the patients who became pregnant conceived spontaneously; no standard forms of assisted reproduction were employed. No patient underwent staging surgery following childbirth in our research.

We run logistic regression to identify factors associated with pregnancy outcomes. Number of chemotherapy cycles was not associated significantly with worse pregnancy outcomes (OR:1.73, 95%CI:0.72-4.15, p=0.214).

Discussion

This retrospective study was carried out at Kasr Al-Aini Hospital - Faculty of Medicine - Cairo University in a time frame of five years, from January 2012 to December 2016. It attempted to learn more about female OMGCTs, how they are treated, and how treatment affects survival and reproductive results. 22 female patients with OMGCTs were recruited in this study.

The patients in this research had a median age of 25 years, which was greater than the 19 years reported by Talukdar et al[8]. Dysgerminoma was the most common histological subtype (40.9%) which is similar to most of the worldwide epidemiological incidence data[4]. Clinical features (swelling and pain/discomfort) and the earlier stage at diagnosis mirrored those described in the literature[3]. In the current research, all of the patients underwent surgery with the intention of preserving their fertility. This is consistent with the published guidelines which state that the best surgical option for patients with germ cell tumors is a unilateral salpingo-oophorectomy that preserves the contra-lateral ovary and the uterus[9].

Although complete cytoreduction could offer survival benefits in selected patients with epithelial ovarian cancer, fertility-preserving surgery and adjuvant chemotherapy in OMGCTs are satisfactory in terms of survival and reproductive outcomes. Patients diagnosed with advanced OMGCTs should have debulking surgery to eradicate the majority of the tumor mass, while avoiding invasive procedures due to the tumors' sensitivity to chemotherapy and high likelihood of successful treatment[10].

Although complete surgical staging with omentectomy and lymphadenectomy was performed in some cases, the Lymphadenectomy in Ovarian Neoplasms (LION) trial found that lymphadenectomy was not associated with improved outcomes, but did result in higher complication and mortality rates and had an additional cost such as extended surgical duration, increased blood loss and blood transfusions, and a need for intensive care unit monitoring[11].

In both the early and advanced stages of OMGCTs, standard therapy is platinum-based combination chemotherapy, with BEP ranking as the first regimen[5]. The study's data are consistent with these standards.

The most popular treatment used was BEP (90.9%) and one patient (mixed choriocarcinoma and dysgerminoma) received EMA-CO. Relapse was documented in only one patient reflecting the excellent prognosis for this disease. She had stage IA dysgerminoma and was treated with BEP as first-line therapy. Twelve months later, she relapsed due to peritoneal disease, but after four cycles of BEP, she established complete remission.

Despite dysgerminomas' high radiosensitivity, no patients in the current research underwent radiation. Radiotherapy is rarely used in the current routine practice since chemotherapy is more efficient, less toxic, and less likely to impair gonadal functioning[4].

The need to identify target mutations for research and therapeutic applications is growing in the quickly changing field of precision medicine. Changes in the genetic makeup of proteins involved in the RAS-RAF-MEK-ERK pathway have been found in several types of tumors, including ovarian cancers. Recently, various inhibitors of this pathway have been created and are now being evaluated for their potential to treat cancer in various clinical trials. The preliminary findings (as many studies are still recruiting participants) of these trials support the role of MAPK in ovarian cancer and propose that MEK inhibitors could be a suitable option for treating this type of cancer[12].

In the last two decades, studies have concentrated on the possibility of target therapies to enhance the survival rate of ovarian cancer patients. Bevacizumab, a highly researched target therapy, is authorized for treating advanced epithelial ovarian, fallopian tube, and primary peritoneal tumors in both first and second lines of treatment. In this retrospective study, no target therapies were used[13].

The overall five-year survival rate was 100%, while the disease-free five-year survival rate was 90%. These results are nearly the same as that reported by A L Husaini et al. in which the overall five-year survival rate was 95.2% and the disease-free five-year survival rate was 88%[14].

Increasing proof has shown the significance of changes in tumor biomarkers for the diagnosis and treatment of ovarian cancer. Recent research on the relationship between tumor biomarkers and chemotherapy in ovarian cancer was analysed by a thorough literature search, offering recommendations for individualised treatment strategies. Despite continued efforts and several suggested tools, there is currently no set treatment plan for advanced ovarian cancer. Future studies should concentrate on broadening the usefulness of biomarkers, reducing resistance, and enhancing the number of actionable biomarkers[15].

In comparison to epithelial ovarian cancer, OMGCT has a considerably better outcome. OMGCT Patients who received adjuvant chemotherapy following fertility-preserving surgical intervention were able to maintain function of their ovaries and retain fertility[16]. This study revealed that 59% of cases had regular menstrual cycle after surgical treatment and chemotherapy.

After cancer treatment, the best timing to get pregnant has not yet been determined. It is preferable to wait six months after chemotherapy since follicle development takes six months[17]. Before attempting conception, we additionally suggest a thorough evaluation of cancer remission. All of the pregnancies in our research happened spontaneously between 7 and 40 months following therapy, without any serious fetal defects, although we still need to do long-term follow-up.

Knowledge acquisition and counseling on reproductive plans are vital for patients with cancer[18]. However, barely half of women who have survived cancer got advice on reproductive health[19]. Unfortunately, our study lacks this information.

We believe that this study is one of the few that provide details on OMGCTs in Egypt regarding clinico-pathological characteristics, survival and reproductive outcomes. Our study also has certain limitations due to its retrospective nature, the small number of patients and single center study. However, it is preferable to follow such a rare disease inside a retrospective research because prospective patient recruitment will take time. Better documentation of our patient records is essential as we were not able to include five more patients due to incomplete data.

Conclusions

The current research has verified that OMGCTs are uncommon tumors that impact young Egyptian females. It also verified the positive outcome of treatment. The fertility-preserving surgery and postoperative chemotherapy for OMGCTs were shown to have satisfactory survival and reproductive results in the current study. However, in order to monitor these patients for the delayed effects of treatments, long-term follow-up is necessary. Multicenter prospective study of this disease's treatment options should be carried out over a number of years with a large number of patients to assess their efficacy and failures. All patients and their families should get educational consultation regarding monitoring and reproductive health.

Compliance with Ethical Standards

Authors' contribution

M.A., H.H.Z.: Conceptualization, resources. M.A.: Data curation, Formal Analysis, writing – original draft. M.A., H.H.Z.: Investigation, methodology. M.A., H.H.Z.: Supervision, validation, Writing – review & editing.

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Study registration

The ClinicalTrials.gov registration number for this study is NCT05905289.

Disclosure of interests

The authors declare that they have no competing interests.

Ethical approval

This study was approved by the Cairo UniversityResearch Ethics Committee, with committee's reference number (N-181-2023).

Informed consent

Oral informed consents were obtained from all patients for publication related data.

Data sharing

The data that support the findings of this study are available from Kasr El-Ainy Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the corresponding author (M.A.) upon reasonable request and with permission of Kasr El-Ainy Hospital.

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References

1. Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY, et al. Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol. 2006;107(5):1075–85. doi:10.1097/01.AOG.0000216004.22588.ce.
2. Saber MM, Zeeneldin AA, El Gammal MM, Salem SE, Darweesh AD, Abdelaziz AA, et al. Treatment outcomes of female germ cell tumors: the Egyptian National Cancer Institute experience. J Egypt Natl Canc Inst. 2014;26(2):103–8. doi:10.1016/j.jnci.2014.03.001.
3. Colombo N, Peiretti M, Garbi A, Carinelli S, Marini C, Sessa C, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2012;23 Suppl 7:vii20-6. doi:10.1093/annonc/mds223.
4. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. Cancer Treat Rev. 2008;34(5):427–41. doi:10.1016/j.ctrv.2008.02.002.
5. Bajorin DF, Sarosdy MF, Pfister DG, Mazumdar M, Motzer RJ, Scher HI, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol. 1993;11(4):598–606. doi:10.1200/JCO.1993.11.4.598.
6. Williams SD, Blessing JA, Hatch KD, Homesley HD. Chemotherapy of advanced dysgerminoma: trials of the Gynecologic Oncology Group. J Clin Oncol. 1991;9(11):1950–5. doi:10.1200/JCO.1991.9.11.1950.
7. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471–4. doi:10.1245/s10434-010-0985-4.
8. Talukdar S, Kumar S, Bhatla N, Mathur S, Thulkar S, Kumar L, et al. Neo-adjuvant chemotherapy in the treatment of advanced malignant germ cell tumors of ovary. Gynecol Oncol. 2014;132(1):28–32. doi:10.1016/j.ygyno.2013.10.009.
9. Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol. 2007 Jul;25(20):2938–43. doi: 10.1200/JCO.2007.10.8738.
10. Di Donato V, Giannini A, D'Oria O, Schiavi MC, Di Pinto A, Fischetti M, et al. Hepatobiliary Disease Resection in Patients with Advanced Epithelial Ovarian Cancer: Prognostic Role and Optimal Cytoreduction. Ann Surg Oncol. 2021;28(1): 222-230. doi: 10.1245/s10434-020-08989-3.
11. Benedetti Panici P, Giannini A, Fischetti M, Lecce F, Di Donato V. Lymphadenectomy in Ovarian Cancer: Is It Still Justified?. Curr Oncol Rep. 2020; 22(3):22. doi: 10.1007/s11912-020-0883-2.
12. Perrone C, Angioli R, Luvero D, Giannini A, Di Donato V, Cuccu I, et al. Targeting

BRAF pathway in low-grade serous ovarian cancer. J Gynecol Oncol. 2024;35(4):

e104. doi: 10.3802/jgo.2024.35.

13. Musella A, Vertechy L, Romito A, Marchetti C, Giannini A, Sciuga V, et al.

Bevacizumab in Ovarian Cancer: State of the Art and Unanswered Questions.

Chemotherapy. 2017;62(2):111-120. doi: 10.1159/000448942.

14. A L Husaini H, Soudy H, El Din Darwish A, Ahmed M, Eltigani A, A L Mubarak M, et al. Pure dysgerminoma of the ovary: a single institutional experience of 65 patients. Med Oncol. 2012;29(4):2944–8. doi:10.1007/s12032-012-0194-z.
15. Tonti N, Golia D'Augè T, Cuccu I, De Angelis E, D'Oria O, Perniola G, et al. The

Role of Tumor Biomarkers in Tailoring the Approach to Advanced Ovarian Cancer.

Int J Mol Sci. 2024;25(20):11239. doi: 10.3390/ijms252011239.

16. Gershenson DM, Miller AM, Champion VL, Monahan PO, Zhao Q, Cella D, et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25(19):2792–7. doi:10.1200/JCO.2006.08.4590.
17. Winkler-Crepaz K, Böttcher B, Toth B, Wildt L, Hofer-Tollinger S. What is new in 2017? Update on fertility preservation in cancer patients. Minerva Endocrinol. 2017;42(4):331–9. doi:10.23736/S0391-1977.17.02633-5.
18. Ethics Committee of American Society for Reproductive Medicine. Fertility

preservation and reproduction in patients facing gonadotoxic therapies: a

committee opinion. Fertil Steril. 2013;100(5):1224–31.

doi:10.1016/j.fertnstert.2013.08.041.

19. Niemasik EE, Letourneau J, Dohan D, Katz A, Melisko M, Rugo H, et al. Patient perceptions of reproductive health counseling at the time of cancer diagnosis: a qualitative study of female California cancer survivors. J Cancer Surviv. 2012;6(3):324–32. doi:10.1007/s11764-012-0227-9.

Table 1: Characteristics of 22 patients with OMGCTs.

Characterstic	N (%)
Clinical Presentation	
Abdomino-pelvic swelling	10 (45.4 %)
Local pain	11 (50 %)
Asymptomatic	1 (4.5 %)
Side	
Right ovary	16 (72.7 %)
Left ovary	6 (27.2)
Pathology	
Dysgerminoma	9 (40.9 %)
Yolk sac tumor	3 (13.6 %)
Immature Teratoma (2 grade III & 3 grade II)	5 (22.7 %)
Mixed	5 (22.7 %)
Clinical Stage	
IA	5 (22.7 %)
IC	5 (22.7 %)
II	6 (27.2 %)
IIIC	5 (22.7 %)
IVA	1 (4.5 %)
Operation type	
Complete staging	9 (40.9 %)
NOT staging	13 (59.1 %)
Elevated tumor markers (pre-surgery)	
LDH	10 (45.4 %)

B-HCG	8 (36.3 %)
AFP	11 (50 %)
CA-125	8 (36.3 %)
Lymphovascular Invasion	4 (18.1 %)
Chemotherapy:	
BEP	20 (90.9 %)
EP	1 (4.5 %)
EMA CO	1 (4.5 %)
Reproductive Outcome	
Normal menstruation	13 (59 %)
Pregnancy/willing to conceive	10/15
Live birth/willing to conceive	8/15
Miscarriage	2
	Median (range)
Age (years old)	25 (14-32)
Size of tumor in max dimensions (cm)	17(3.5-28)
Follow-up duration (months)	48(24-84)
Chemotherapy courses	3(1-5)

Abbreviations: LDH: Lactate dehydrogenase, B-HCG: Beta human chorionic gonadotropin, AFP: Alphafetoprotein, BEP: Bleomycin – etoposide – platinum, EP : Etoposide – platinum. EMA-CO : Etoposide-methotrexate-dactinomycin, cyclophosphamide-vincristine

Figure 1. Disease-free survival (DFS) of OMGCTs patients.