



Fertility-preserving surgery for advanced stage ovarian germ cell tumors

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HIGHLIGHTS

- Rate of uterine preservation among women with advanced stage MOGCTs was 79.8%.
- Uterine preservation was not associated with a decreased survival.
- FSS should be considered in women with advanced stage MOGCTs interested in future fertility.

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ABSTRACT

Objective. To evaluate the prevalence and safety of uterine preservation among premenopausal women diagnosed with a malignant ovarian germ-cell tumor (MOGCT) of advanced stage (stage II–IV).

Materials and methods. The National Cancer Database was accessed and a cohort of women aged <40 years, diagnosed with a MOGCT were identified. Those with stage II–IV disease who underwent cancer-directed surgery and received chemotherapy were selected for further analysis. Performance of hysterectomy was assessed from site-specific surgery codes. Overall survival (OS) was determined following generation of Kaplan–Meier curves and compared with the log-rank test. A Cox multivariate model was constructed to control for possible confounders.

Results. A total of 526 eligible patients were identified; rate of hysterectomy was 20.2%. Women who had a hysterectomy were older (median age 30.5 vs 20 years, $p < 0.001$) and more likely to present with bilateral tumors (12.6% vs 3.8%, $p < 0.001$). No differences were noted based on tumor histology ($p = 0.67$). Rate of uterine preservation was 82.8%, 79.5% and 75% for those with stage II, III and IV disease respectively ($p = 0.46$). There was no difference in OS between women who had hysterectomy and those who did not ($p = 0.051$); five-year OS rates were 87.1% and 94.4% respectively. After controlling for disease stage, tumor histology and patient race, uterine preservation was not associated with a decreased survival (HR: 0.59, 95% CI: 0.28, 1.24, $p = 0.19$).

Conclusions. Uterine preservation was not associated with decreased survival and should be considered in women with advanced stage GCTs interested in future fertility.

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1. Introduction

Malignant ovarian germ-cell tumors (MOGCTs) represent approximately 2–3% of all ovarian tumors [1]. Contrary to the more prevalent epithelial carcinomas, their incidence peaks during childbearing age [1,2]. As such the majority of women diagnosed with MOGCTs may wish to retain their reproductive potential. Standard management of MOGCT includes surgical removal of the affected ovary and

administration of adjuvant chemotherapy [1,3]. Due to the sensitivity of these tumors to platinum-based chemotherapy, overall survival rates are excellent even for women with advanced disease [4,5]. The oncologic safety of fertility-preserving surgery (unilateral salpingo-oophorectomy and uterine preservation) for women with early-stage disease has been extensively evaluated and is currently the gold standard [1,3,4]. Given the chemosensitivity of MOGCTs, the practice of fertility-preserving cytoreductive surgery has also been extrapolated and applied to women with advanced stage disease [6]. However, evidence on its safety is sparse and derives from single-institutional retrospective studies. In the present study we investigated the prevalence and safety of uterine preservation among young premenopausal women (age < 40 years) diagnosed with advanced stage (II–IV) MOGCTs, using a multi-institutional, hospital-based database.

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2. Materials and methods

A cohort of women diagnosed between 2004 and 2014 with a malignant ovarian germ-cell tumor (MOGCT) (ICD-O-3 histology codes 9060/3–9102/3) was drawn from the National Cancer Data Base (NCDB). The NCDB, established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, is a hospital-based database capturing approximately 70% of all malignancies diagnosed in the United States. Patient data are prospectively collected from participating commission-accredited cancer programs and are frequently audited to ensure their high-quality [7]. All data are de-identified and available for research purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data.

In the present study, women without histologic confirmation, aged ≥ 40 years and with unknown pathological disease stage were excluded. Patients with advanced stage disease (II–IV) who underwent cancer-directed surgery and received chemotherapy were selected for further analysis. Based on site-specific surgery codes the performance of hysterectomy was evaluated; women with unknown hysterectomy status were excluded. We opted to exclude cases with the surgery code “debulking; cytoreductive surgery” given the fact that we could not verify whether or not a hysterectomy was performed. Fig. 1 depicts the patient selection flow-chart.

Demographic, clinico-pathological, and treatment variables were extracted from the de-identified NCDB dataset. Patient race was recoded into White, Black, Asian/Native American/Pacific Islander and Other/Unknown while age was grouped as premenarchal/adolescent (≤ 19 yrs) and young adults (20–39 yrs). Based on ICD-O-3 histology codes, cases were categorized into the following histological groups: dysgerminoma (9060/3–9064/3), yolk-sac tumor (9071/3), immature

teratoma (9080/3–9084/3), mixed germ cell tumor (9085/3) and other. Performance of lymph node sampling/dissection (LND) was evaluated from the “regional lymph node surgery” variable. For analysis purposes year of diagnosis was dichotomized into 2004–2009 and 2010–2014.

Observed survival (OS) was defined as the months elapsed from tumor diagnosis to the date of death or last-follow up. Kaplan-Meier curves were generated to determine 5-year OS rates while univariate analysis was performed with the log-rank test. In addition, a Cox hazard regression analysis was performed to examine the effect of uterine preservation on overall mortality after controlling for possible confounders. Variables significantly associated with OS in univariate analysis were entered in the multivariate model. Vital status and months from tumor diagnosis to the date of last contact or death are suppressed for cases diagnosed in 2014, as such survival analyses were restricted to cases diagnosed in 2013 and earlier. Frequency of distribution of categorical variables was compared with the chi-square test or Fisher's exact test and continuous variables with Mann-Whitney *U* test. All statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY) and the alpha level of statistical significance was set at 0.05. The Joinpoint Regression Program 4.4.0 provided by the National Cancer Institute was used to evaluate and visualize a possible temporal or age-related trend in the use of uterine preservation [8]. The rate of uterine preservation was depicted as a function of calendar year or patient age following log transformation while the presence of inflection points, indicating a change in the trend, was evaluated using the permutation test.

3. Results

A total of 526 eligible patients, managed in 288 institutions were identified. The median number of cases reported by a facility was 2; 33.7% of patients were treated in institutions that had reported only a single case while 37.7% and 28.6% were managed in facilities that reported 2–3 and >3 cases respectively. Median patient age was 21 years (range 2–39); the majority was of White race (75.7%) while 15.4% and 5.5% were Black and Asian respectively. Most women had stage III disease (65%); 24.3% and 10.6% had stage II and IV disease, respectively. The most common histologic subtypes were dysgerminoma (42.4%) and immature teratoma (22.4%) followed by mixed germ cell tumors (16.9%) and yolk sac tumor (15.8%). As assessed from the Charlson/Deyo score, presence of medical co-morbidities (score ≥ 1) was infrequent (7%).

Overall, rate of uterine preservation was 79.8%. It was comparable between the two study periods (77.6% and 82.3% for patients diagnosed between 2004 and 2009 and 2010–2014, respectively, $p = 0.18$) while a non-statistically significant increase was observed (annual percentage change; APC: 1.4, 95% CI: $-0.4, 3.3$). Women who did not undergo hysterectomy were younger (median age 20 vs 30.5 years, $p < 0.001$) and a decrease in the rate of uterine preservation was noted following the age of 26 years (Fig. 2). Lower rates of uterine preservation were observed among Black women (69.1%) compared to White (80.9%), Asian (89.7%) and Other/Unknown race (88.9%), $p = 0.034$. After controlling for patient age, Black women were more likely to undergo hysterectomy (HR: 2.46, 95% CI: 1.38, 4.39) compared to White women. No differences were noted based on patient volume of reporting facility ($p = 0.65$), insurance status ($p = 0.095$), median income ($p = 0.19$) or presence of medical co-morbidities ($p = 0.3$). Rates of uterine preservation were comparable among the different histologic subtypes of MOGCTs; 81.2% for women diagnosed with dysgerminoma, 77.1% with immature teratoma, 75.9% with yolk-sac tumor, 83.1% with mixed germ-cell tumor and 84.6% with other subtypes, $p = 0.67$. Moreover, similar rates of uterine preservation were observed across disease stages (stage II: 82.8%, stage III: 79.5% and stage IV: 75%, $p = 0.46$). However, women who underwent hysterectomy were more likely to present with bilateral tumors (12.6% vs 3.8%, $p < 0.001$). Rates of LND were similar between

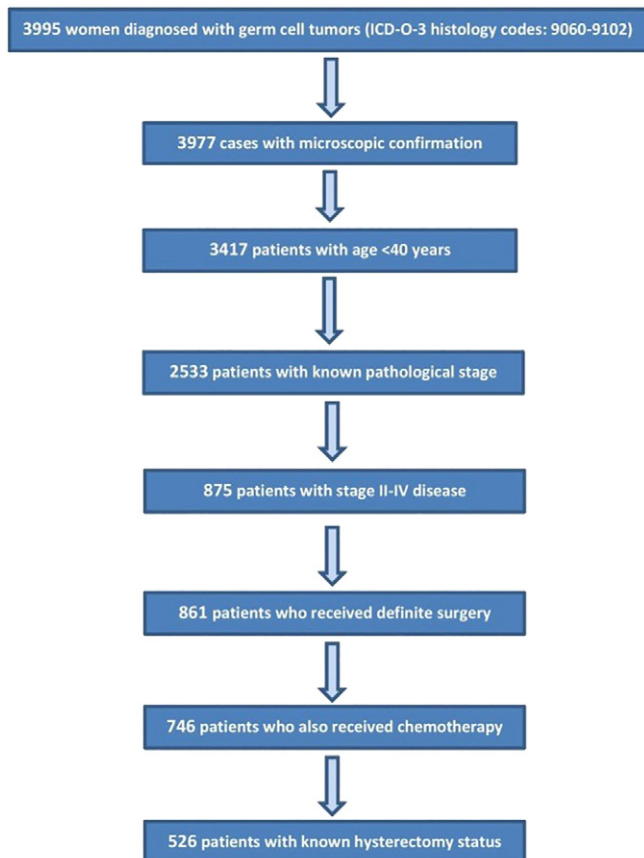


Fig. 1. Patient selection flow-chart.

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