

Original Article

Running Title: Non-epithelial Ovarian Tumor Survival Rate in Iran

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Survival Rate of Non-epithelial Ovarian Tumors in Iran

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Abstract

Background: The aim of this study was to estimate the overall survival and relapse free survival (RFS) of the non-epithelial ovarian tumors (NEOTs) of ovarian germ cell tumors (OGCT) and ovarian sex cord tumors (OSCT) in Iranian women; we also evaluated the relative prognostic factors.

Method: In this retrospective study, we screened the documents of all the women diagnosed with OGCTs and OSCTs from 2012 to 2019. We further assessed the overall survival (OS), relapse free survival (RFS), and different prognostic factors.

Results: A statistically significant association existed between RFS and stage of the disease at diagnosis in OSCTs group by univariate analysis and multivariate analysis (HR: 0.25 (95% CI (0.08-0.78), p-value: 0.01) and multivariate analysis (HR: 0.27 (95% CI (0.08-0.97), p-value: 0.04), respectively. The kaplan-meier analysis and the Log Rank (Mantel-Cox) showed a statistically significant relationship between the stage at diagnosis and RFS in OGCT group (P -value=0.042). RFS was 96% for OGCT patients, and 92.7% for OSCT patients. During the follow-up, only one patient passed away in the dysgerminoma group; the OS rate was 98% for OGCT patients, and 100% for OSCT patients.

Conclusion: The overall survival and RFS obtained in this study confirmed that the ovarian germ cell and sex cord malignancies were among the highly treatable solid tumors. Stage can be proposed as the main prognostic factor; also, larger series of studies are needed for detecting the prognostic significance of serum markers.

Keywords: Survival, Ovarian cancer, Germ cell ovarian tumor, Sex cord ovarian tumor

Introduction

Almost 10-15% of all ovarian cancers are non-epithelial ovarian tumors (NEOT); they consist of the most common malignancies of germ cell origin (OGCT) and sex cord-stromal cell origin (OSCT); each of them comprise a broad spectrum of sub-types that differ based on their clinical presentation, tumor biology, and histology.¹ Dysgerminoma, non-gestational choriocarcinoma, yolk sac tumor, mature teratoma, immature teratoma, embryonal carcinoma, mixed germ cell tumor, and endodermal sinus tumor make up different types of ovarian germ cell tumors (OGCTs) according to World Health Organization (WHO) classification.² Ovarian sex cord tumors (OSCTs) are a heterogeneous group of NEOTs; they cover various sub-type tumors, including granulosa as the most frequent type (adult-type granulosa, juvenile-type granulosa), theca-fibroma, thecoma, fibroma, fibrosarcoma, sertoli or sertoli-lydig cell neoplasm, and gynandroblastoma.³ Ovarian cancers have shown a wide range of age occurrence from childhood to old age. OGCTs represent 5% of all ovarian neoplasms; they mostly occur in women under 30 years of age; OSCTs comprise 3%–5% of ovarian malignancies; they are usually diagnosed in women of all ages; however, they mainly occur in the fourth and fifth decades of age, middle age, and postmenopausal women.^{4, 5} OGCTs occur in both females and males; however, it is more prevalent and usually benign in females and more malignant in males with an incidence rate of malignant type 7–8/100,000 in men and 3.7/1 000 000 in women.^{1, 3, 6}

Pelvic pain, feeling of pelvic pressure because of a pelvic-abdominal mass, abdominal distension, vaginal bleeding, and menstrual irregularities are among the initial symptoms and signs of NEOTs; they are diagnosed through pelvic ultrasound, abdominopelvic computed tomography (CT) scan, chest

X-ray, and positron emission tomography (PET) scan. Serum alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and Inhibin B levels are some nonspecific tumor markers; these markers provide prognostic information and should be measured in the diagnostic procedure of NEOTs.⁷

Clinical prognosticators are not fully defined in ovarian OGCTs; however, factors such as age at diagnosis, tumor stage, extent of surgical resection, and tumor histology are primarily assessed.⁸ Based on ESMO Clinical Practice Guidelines 2018, follow-up visits must include history, physical examination with pelvic examination, and tumor markers every three months for the first two years and every six months during the third, fourth, and fifth year or until progression. A pelvic ultrasound should be carried out every six months in patients undergoing fertility-sparing surgery; meanwhile, a CT-scan of the abdomen and pelvis is carried out according to clinical indication.³

The objective of this study was to estimate the overall survival and RFS of the NEOTs related to OGCTs and OSCTs in Iranian women and evaluate the relative prognostic factors.

Materials and Methods

This is a retrospective study, and all patients were referred to the academic oncology center of Mashhad University; we performed the census method and enrolled all patients referred to our center. The Ethics Committee and Institutional Review Board approved the study protocol (ethics code: 980075). We recorded the documents of all the women with OGCTs and OSCTs who were diagnosed from 2012 to 2019. We determined the histological type based on WHO's classification. Patients were divided into two groups, namely OGCT and OSCT. The OGCT group included those affected by dysgerminomas, endodermal sinus tumors, and immature

teratoma; patients with granulosa and thecoma tumors belonged to the OSCT group. Surgery, as the initial treatment, included optimal surgery (complete resection of the tumor) with fertility preserving (fertility-sparing surgery was defined as a uterine and ovary preserving procedure), optimal surgery without fertility preserving, and non-optimal surgery (incomplete resection of the tumor). Patients underwent surgical staging after diagnosis; in OSCT group, patients with stage 2 and above, and in OGCT group, all cases of yolk sac tumor, immature teratoma grade 1 with ascites, grade 2, 3 and dysgerminoma except stage 1a received chemotherapy regimen BEB 3 or 4 courses depredate to the stage of the disease (Bleomycin-Etoposide Cisplatin). Follow-up was based on the 2018 Guidelines of ESMO as already mentioned above.

Detailed data regarding patients' demographic information, clinical signs at presentation and diagnosis, the histologic type of tumor, stage at presentation, serum tumor marker levels, type of surgery, recurrence date, follow-up, death, and survival were collected and reviewed retrospectively from medical and surgical documents and pathology reports.

Statistical analysis

Patients' population characteristics were assessed by descriptive analysis. We defined overall survival (OS) as the period from the initial diagnosis until death. Relapse-free survival (RFS) was defined as the time duration between primary diagnosis and first evidence of disease recurrence. We used Kaplan-Meier method and the log-rank test to obtain and compare the OS and RFS curves. Univariate long rank (mantel cox) test evaluated the relationship between different factors and DFS. Using the Cox regression analysis, we performed the multivariate analysis to evaluate the relative significance of various prognostic

factors only for variables with $P < 0.05$ following univariate. Statistical analyses were all carried out based on the Statistical Package for the Social Sciences software program version 15.0 for Windows. All P -values were two-sided. Differences at $P < 0.05$ were considered as statistically significant.

Results

Clinicopathological characteristics

Table 1 summarizes the characteristics of the patients at diagnosis.

In total, we enrolled 102 patients with NEOTs including OGCTs and OSCTs. Of the included patients, 47 were diagnosed with OGCTs, 17 (36.1%) with immature teratoma, 6 (12.7%) with endodermal sinus tumor, and 24 (51%) with dysgerminoma. Of the 55 patients identified with OSCTs, 50 (90.9%) had the granulosa type, and 5 (9.1%) had the thecoma type tumor. The mean ages of the OSCT and OGCT patients were 46 years (14-84 years) and 23 years (9-46 years), respectively. We performed the census method and included 102 patients referred to our center. 58 patients (more than 50%) were older than 30 years. Patients' symptoms at diagnosis were as follows: pain in 26 (55.3%) of the germ cell tumor patients and 35 (63.6%) of the sex cord tumor patients. We detected ascites in imaging in seven patients (14.9%) with germ cell tumor and six patients (10.9%) with sex cord tumor. We also found mass in imaging in 46 (97.9%) of the germ cell tumor patients and 53 (96.4%) of the sex cord tumor patients. Among the symptoms of the disease, ascites was higher in patients with stage 3 and above. However, based on imaging mass, the most common symptom was abdominal and pelvic pain and discomfort. Stage distribution assessment showed that 45 (81.8%) of the patients with OSCTs were at stage 1 or 2 and only 10 (18.2%) were at stage 3 and more at diagnosis. However, 33 (70.1%) of the patients with OGCTs were at stage 1 or 2 at diagnosis and 14 (29.2%) were at

stage 3 or more. We performed surgical staging surgery as the initial treatment for all the study population as optimal cytoreductive surgery with fertility preservation in 63.7% of all the ovarian cancer patients. Bilateral salpingoophorectomy was performed in 10/6 of the patients with OGCTs, and 50/9 of OSCT patients. We conducted optimal cytoreductive surgery without fertility preservation in 32.4% of patients and non-optimal surgery in 3.9% of the patients. We performed fertility preservation in 66 patients and surgery without fertility preservation in 32 patients; four patients underwent nonoptimal surgery. In the group with surgery without fertility preservation, four cases belonged to the OGCT group; they were over 42 years old and were complete family members. In OSCT group, four nulliparus patients underwent surgery without fertility preservation. But, they had infertility and were near menopausal age. This was expected in 28 patients of OSCT surgery without fertility preservation due to their higher mean age. The following received chemotherapy (3-4 cycle BEP regimens): 10 patients with OSCT that were in stage 2 and higher and 20 patients in group OGCT (six patients with yolk sac tumor, eight with immature Teratoma grade 2 and 3, and six with dysgerminoma stage 1b and higher).

Survival analysis

The median follow-up duration was 59 months (9-84 months). During this period, we observed recurrence in six out of the 102 included patients with NEOC, two with dysgerminoma type of OGCTs, and four with granulosa type of OSCTs. In five patients, we detected recurrence during the first two years of follow-up; in one patient, recurrence was observed in the third year of follow-up. We estimated relapse free survival at 94.3% for all the NEOC patients,

96% for OGCT patients, and 92.7% for OSCT patients.

During this follow-up period, only one of the included patients died from dysgerminoma; the overall survival of all NEOT patients was estimated at 99% for all the NEOC patients, 98% for OGCT patients, and 100% for OSCT patients.

Prognostic factors

Univariate analysis showed a statistically significant association between RFS and disease stage at diagnosis only in OSCT group (HR: 0.25 (95% CI (0.08-0.78), $P=0.01$).

Based on multivariate analysis, a statistically significant relationship existed between stage at diagnosis and RFS of patients in the OSCT group (HR: 0.27 (95% CI (0.08-0.97), $P=0.04$). The Kaplan-Meier analysis and the LogRank (Mantel-Cox) showed a statistically significant association between stage at diagnosis and RFS in OGCT group ($P=0.042$); however, univariate analysis did not reveal any significant relationship between RFS and disease stage in OGCT group (HR: 0.07 (95% CI (0.00-0.51), $P=0.4$). Figures 1 and 2 show the Kaplan-Meier graphs for OSCTs and OGCTs, respectively.

The survival analysis showed no statistically significant association between RFS and tumor histology, patients' age, and type of surgery.

We measured inhibin level at diagnosis in 37 of the sex cord tumor patients; moreover, a statistically significant correlation was obtained between inhibin level and tumor recurrence in patients with granulosa type of OSCTs (HR: 1.001, 95% CI (1-1.001), $P=0.023$).

We measured LDH in 28 of the patients with germ cell tumor; there was no statistically significant relationship between LDH and tumor recurrence in patients with OGCTs (HR: 1, 95%CI (0.999-1.001), $P=0.47$).

We also measured AFP and BhCG in 32 and 26 of the patients with OGCTs, respectively; however, there was no statistically significant association between AFP (HR: 1, 95%CI (1-1), $P=0.95$) and BhCG (HR: 1, 95%CI (1-1), $P=0.83$) and tumor recurrence in these patients.

Discussion

In this study, we evaluated three types of sex cord-stromal cell origin tumors; granulosa and thecoma were the most and least prevalent types, respectively. In the OGCT group, endodermal sinus tumor and dysgerminoma were the least and most common types.

Based on our results, overall survival and RFS were 98% and 96% for OGCT and 100% and 92.7% for OSCT groups, respectively; this shows that standard and conservative surgeries and adjuvant therapies did not compromise the survival rate of the NEOC patients.

The overall survival in this study was high; this indicates the increasing survival rate of patients with OGCTs owing to the improvement in treatment technologies and use of radioisotopes and postoperative radiation therapy.^{6,9}

OGCTs have shown excellent prognosis if managed with standard initial treatments;¹²⁻¹⁴ the long-term outcome of patients with 10- and 25-year survival rates of 81% and 81% have also been favorable.¹⁵

Our results are similar to previous studies regarding the most common type of tumor in NEOT.⁸⁻¹¹ The majority of the patients in previous studies were at stage I at diagnosis;^{16,17} similarly, 74.5% of all included patients in the present study were at stage I and II at diagnosis.

We proposed advanced stage at diagnosis as a major prognostic factor in OSCT group (HR: 0.064, 95%CI (0.07-0.618), $P=0.017$); this confirms the previous results that suggested the early-stage disease as an important predictor for improved survival.^{18,19} Kaplan-Meier

analysis showed a statistically significant association between stage at diagnosis in OGCT group and RFS ; however, this correlation was not confirmed by univariate and multivariate analysis. Previous publications proposed the early stage of the disease as a significantly favorable prognostic factor regarding RFS.^{12,15} The overall survival of OGCT patients at stage I and II was 100% and that of patients at stage III and higher was 88.2%. For OSCTs, RFS rate of stage (I-II) and III was 97.8% and 70%, respectively; thus, higher stages at diagnosis can be regarded as a major prognostic factor with poor prognosis. As an OSCT serum marker, inhibin was another factor with a significantly poor prognostic value for granulosa tumors; it has been recommended to be assessed during the follow-up period in premenopausal and postmenopausal women.^{20,21} The tumor markers of CA125, AFP, and BhCG were evaluated in the germ cell tumors. Similar to one previous study, we were unable to identify a prognostic value for any of the evaluated serum markers in OGCT group;⁸ this might be attributed to the population size of our study. Mangili et al. showed that the pretreatment of AFP or BhCG serum levels was not associated with survival when evaluated alone; however, univariate and multivariate analyses confirmed a significant correlation with survival when the two tumor makers were assessed together.⁸ There has been an increase in the use of fertility conserving approaches; these methods have shown favorable results for the treatment of germ cell and sex cord ovarian cancers.²² There was no statistically significant difference between the RFS of patients undergoing fertility sparing surgery and those with optimal surgery and fertility sparing or non-optimal surgery; however, the increased rate of fertility sparing surgery over time, showed that as a safe and feasible approach it will not compromise the survival of patients.²³

We did not find any significant association between the type of surgery and OS and RFS; however, with overall survival rates of 99% for all patients and 98.5% for patients with fertility sparing optimal surgery, our results were similar to other studies. Previous studies reported a good prognosis for NEOTs and excellent survival and RFS rates by performing standard conservative surgical resection and treatments during the follow-up periods.^{11, 14, 24-27} Comparison of these trials is challenging because of the considerable heterogeneity in clinicopathologic and therapeutic approaches and characteristics, including stage distribution at diagnosis, histologic type of tumor, surgical management and chemotherapy treatment.

Young women are mainly affected by OGCTs, and the peak of the tumor incidence is around 20 years of age;^{16,28} we also showed that the mean age of the patients was 25 in the OGCT group and 46 in the OSCT group. In some studies, more than 30 years of age was proposed as a risk factor for recurrence, affecting disease prognosis and predicting poor survival.^{8,18,19,22} In this study, multivariate and univariate analyses did not confirm the prognostic value of the age in any of the studied groups of ovarian cancers, which is in line with another previous report.¹⁵ A similar study in Italy investigated the disease stage, treatment, and follow-up in patients with NEOTs.²⁹ Another study in the Netherlands reported non-epithelial ovarian tumors, incidence, and survival between 1989-2015; they identified a total of 1258 non-epithelial ovarian tumors comprising 752 GCTs (60%), 341 SCSTs (27%), and 165 sarcomas (13%). Approximately 97% of patients underwent surgical resection for the primary tumor, 31% received systemic treatment, and 3% underwent radiotherapy. Between the late 1980s and 2015, the five-year overall survival improved in all histologic subtypes.³⁰

In summary, the overall survival and RFS obtained in our study confirmed that the ovarian germ cell and sex cord malignancies were among the highly curable solid tumors with almost complete response to treatment. Stage can be proposed as the main prognostic factor; larger series of studies are required for detecting the prognostic significance of GCTs serum markers. Our study had some limitations. We only included patients with ovarian cancer in our referral center (northeast of Iran); therefore, we were not able to assess the prevalence of ovarian cancer and NEOT in Iranian women. However, we obtained OS and RFS of NEOT and evaluated the relative prognostic factors in these patients. Due to the limited data on NEOT management, careful evaluation is of utmost importance.

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Conflicts of Interest

None declared.

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Table 1. Summarized characteristics of the patients

Age	Mean (range)
GCT	23 (9-46)
SCT	46(14-84)
Stage at presentation	N(%)
GCT	
I and II	34 (66.7)
III and more	17 (33.3)
SCT	
I and II	45 (81.8)
III and more	10 (18.2)
Histologic subtype	N(%)
GCT	
Teratoma	17(36.1)
Endodermal sinus tumor	6(12.7)
Dysgerminoma	24(51)
SCT	
Thecoma	5(9.1)
Granulosa	50(90.9)
Surgery	
GCT	
Optimal with fertility preserving	43 (91.5%)
Optimal without fertility preserving	4 (8.5%)
SCT	
Optimal with fertility preserving	23 (41.8%)

SCT: sex cord tumor

GCT: germ cell tumor

Survival Functions

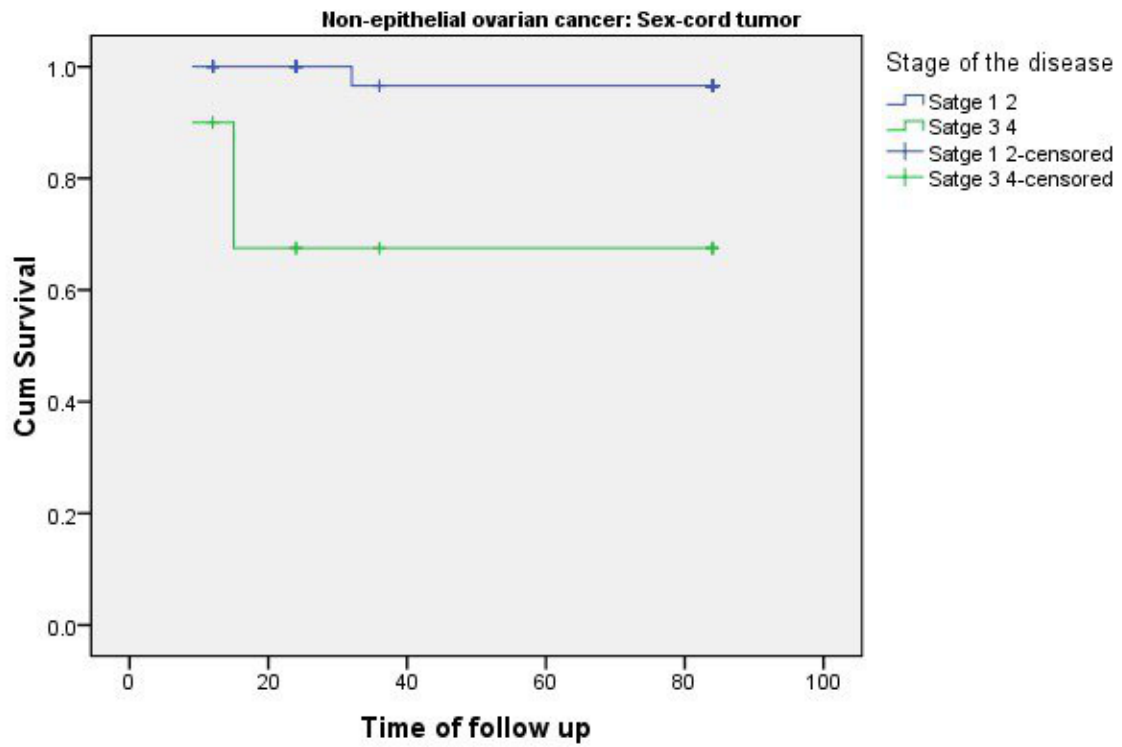


Figure 1. Kaplan-Meier estimate of relapse-free survival in sex cord tumors by stage.

Survival Functions

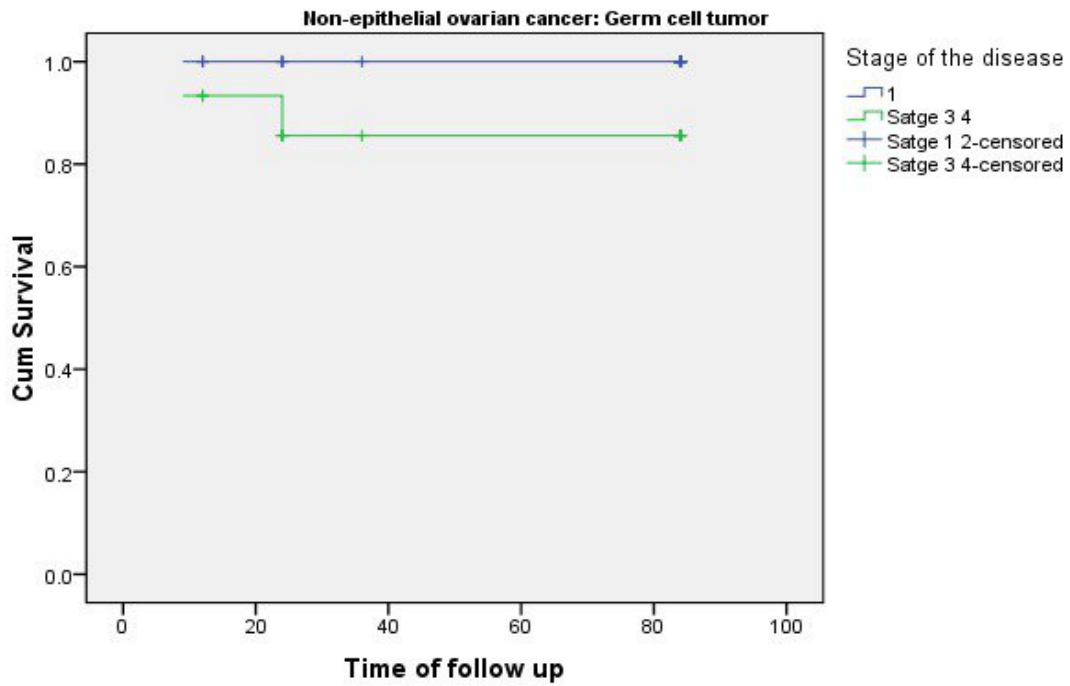


Figure 2. Kaplan-Meier estimate of relapse-free survival in germ cell tumors by stage.