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RESEARCH ARTICLE

Insights into the Clinico-Epidemiological Aspects of Non-Epithelial Ovarian Tumor Emphasizing Diagnosis and Tailored Surgical Approach: A Single Institutional Retrospective Study

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ABSTRACT

Background: Ovarian cancers account for approximately 27% of all female tumors, with non-epithelial ovarian cell carcinoma being rare at around 10% of overall ovarian cancer cases. The aim of this study is to recognize the prognostic factors Reporting survival outcome in the form of OAS, DFS, and PFS. **Aim and Objectives:** The aim of the study is: Defining the lines of treatment have been uses and recognize the prognostic factors Reporting survival outcome in the form of OAS, PFS, and DFS. **Patients and Methods:** This study included fifty-six patients, who had recruited in the period between January 2005 and December 2020 with the following criteria: Proven non-epithelial ovarian carcinoma, all stages, age greater than 18 years. All statistical analyses will be performed using a software tool (SPSS) (statistical package for social sciences) version 26. Quantitative data will be summarized as medians & minimum-maximum values (range) or mean & standard deviation, while qualitative data as percentages. The results will be considered significant if the p-value was < 0.05. **Results:** all 56 patients (100%) underwent surgery: 96.4% had upfront early debulking, and 3.6% had interval debulking post-neoadjuvant chemotherapy. Fertility Sparing Surgery was performed in 50%, optimal debulking in 41.4%. Surgical debulking left no residual disease in 78.6% (44 patients); 12 patients had residual disease (R1 or R2). Chemotherapy was administered to 55.4% of patients, with 67.7% receiving the BEP regimen and 9 patients receiving other regimens. Pathological responses in 12 patients with residual disease 75% achieved complete response. After a median follow-up of 61 months (20 to 200 months), the study found a median (OAS) of 66 months (22-201 months). The 5-year OAS rate was 94.6% for 53 patients. Median (PFS) was 66 months (15-201 months), with a 5-year PFS rate of 85.7% for 48 patients. Among 44 completely treated patients, (DFS) was 83 months (range: 24-201 months), with a 5-year DFS rate of 93.2% for 41 patients. (Supplementary table is available). **Conclusion:** According to the data presented in this study, by univariate analysis; performance status, stage, type of surgery, and tumor residual after debulking surgery were significant prognostic factors for survival**.**

Keywords: Non-epithelial ovarian cancer, Malignant ovarian germ cell tumors, Sex cord-stromal tumors, Epidemiology, Prognosis; Survival

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INTRODUCTION

Problem

Ovarian cancers represent about 27% of all tumor in female. Non epithelial ovarian cell carcinoma is rare which is about 10% of the overall ovarian cancers (Thomakos et al., 2018). According to WHO classification in 2014 (https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Female-Reproductive-Organs-2014) of non-epithelial ovarian cancer for most common types includes germ cell tumors, sex cord stromal tumors, mesenchymal tumors and miscellaneous tumors.

Cancer stage stands out as the most crucial factor in determining cancer prognosis as well as to guide postoperative treatment recommendations (Miller et al., 1997). The standard surgical approach for treatment of these ovarian cancer types is open laparotomy, although, minimally invasive surgery (MIS) of traditional and robot-assisted laparoscopy has been primarily explored in ovarian cancer patients with stage I or II cancer where extensive cyto-reduction may not be required (Lawrie et al., 2013, Park et al., 2013, Lucidi et al., 2017). For most ovarian cancer patients, adjuvant systemic treatment is recommended, with the most commonly utilized are platinum-based regimens as bleomycin, etoposide plus cisplatin (BEP) and paclitaxel plus carboplatin (PC) (Brown et al., 2004).

Unfortunately, most ovarian cancer recurrences manifest within two years of initial therapy. The main determinant prognostic factors for germ cell tumors are cancer stage and surgical resection. However, the determinant prognostic factors for sex cord stromal tumors are the presence of intraperitoneal tumor rupture and high preoperative CA-125 level. In addition to cancer stage, calcium level, surgical resection, and tumor size, the presence of large cells is an imp. prognostic factor in small cell hypercalcemic ovarian cancer type (Ray-Coquard et al., 2018).

The overall 5 years-survival rate (OAS) is 85% in germ cell tumors, 97% in sex cord stromal tumors, and in small cell hypercalcemic ovarian cancer only two-year survival, which is less than 35% (Zhang et al., 2017, Lang et al., 2018).

Study Aim

Defining lines of treatment used for non-epithelial ovarian cancer patients in a single-center study retrospectively and analyze the various prognostic factor(s) related-to or affecting patients' survival outcome; either overall survival or progression free survival.

PATIENTS, METHODS and DATA

Study type: Retrospective study based on hospital records of patients with non-epithelial ovarian tumors treated at the Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, Faculty of Medicine, Mansoura University, Mansoura, Egypt, between January 2005 to June 2020.

Ethical Approval: This study was approved by the Ethical Committee of the Faculty of Medicine, Mansoura University, Mansoura, Egypt, approval # for year 2004.

Patients

Inclusion criteria: Proven non-epithelial ovarian carcinoma, all ovarian cancer stages, patients age greater than 18 years.

Exclusion criteria: Patients with double malignancy or epithelial ovarian carcinoma. Data collected for all participants during the specified time period Clinical assessment of the patients' age, presence of comorbidities, complaints, and complaints duration before presentation, menstrual status, history of previous therapy, and family history of ovarian cancer or any cancer. Clinical examination, including symptoms, signs, and performance status evaluated according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale (ECOG PS) (Oken MM, 1982).

Documented investigations, including pathological reports, laboratory tests of complete blood count (CBC), liver function tests, alkaline phosphatase, serum creatinine, serum tumor markers; cancer antigen125 (CA125), alpha-feto protein (AFP), and beta-human Chorionic Gonadotropin (b-hCG), lactate dehydrogenase (LDH) enzyme level, and radiological assessments of abdominal ultrasound (US), abdominal computed tomography (CT) or magnetic resonance imaging (MRI), CT chest, bone survey or scan, and brain MRI when indicated.

Disease characteristic pathological type and stage

Treatment Options: According to the timing of debulking, primary debulking where surgery is followed by adjuvant chemotherapy, interval debulking where surgery was done after neoadjuvant chemotherapy. The standard staging (optimal debulking) procedure consists of peritoneal cytology (washings or ascites). Visual assessment of the upper abdomen, peritoneal surfaces, and large and small bowel mesentery and other abdominal organs, with

biopsies of abnormal findings. Hysterectomy with bilateral salpingo-oophorectomy. Pelvic and paraaortic lymph node dissection. Infra-colic or infra-gastric omentectomy, if unilateral salpingo-oophorectomy is being considered. Full surgical staging, including washings, omentectomy, pelvic, and paraaortic lymphadenectomy, and peritoneal biopsies. Thorough abdominal exploration and biopsy of any abnormal areas. Endometrial biopsy to exclude synchronous endometrial cancer.

Mode of Surgery: Open laparotomy, minimally invasive surgery, Robotic-assisted.

Chemotherapy: Neo-adjuvant chemotherapy given before surgical intervention, adjuvant chemotherapy given after surgical intervention, and first-line chemotherapy given after recurrence or progression. Radiotherapy is palliative radiotherapy for metastatic disease to bone 30Gy/5Fx.

Assessment of Response to Treatment and Adverse Events During Treatment was done. Tumor response was evaluated every three cycles by baseline and repeated assessment using imaging studies (abdomino-pelvic CT scan or MRI, chest CT scan, and X-ray) according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse et al., 2000). Complete response (CR) was defined as the disappearance of all lesions for at least four weeks. Partial response (PR) defined as a reduction of >30% in the sum of the longest diameters of lesions, and progressive disease (PD) was an increase of >20% in the sum of the longest diameters of lesions, while stable disease (SD) was defined as measurable disease that remained the same and did not meet the criteria of CR, PR, and PD.

Symptoms and signs of treatment toxicities were assessed, including hematological toxicities (anemia, neutropenia, and thrombocytopenia) or non-hematological toxicities (e.g., nausea, mucositis, vomiting, diarrhea, and peripheral neuropathy). Toxicities were reported according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Follow-up data were obtained from the patients' medical records every three cycles of chemotherapy and after the end of treatment by clinical examination, tumor marker, and/or with CT/MRI Pelvic-abdominal with contrast every three months for the first year, then annually.

In Silico Analysis and Bioinformatics Search

The ovarian cancer databases

According to Kyoto Encyclopedia of Genes and Genomes (KEGG) (Release 108.1, November 1, 2023) Accessed Dec. 16th, 2023. ovarian carcinogenesis https://www.genome.jp/entry/H00027.

The human protein atlas describes various types and statistics of ovarian cancer https://www.proteinatlas.org/humanproteome/disease/ovarian+cancer#ovarian_cancer and https://www.proteinatlas.org/learn/dictionary/pathology/ovarian+cancer. The ovarian cancer gene database accessed Dec. 18th, 2023 https://ocgene.bioinfo-minzhao.org/index.html.

Cancer Statistics Explorer Network SEER*Explorer by the NCI, NIH Accessed Dec. 18th, 2023

https://seer.cancer.gov/statistics-network/explorer/application.html?site=61&data_type=4&graph_type=2&compareBy=stage&chk_stage_101=101&chk_stage_104=104&chk_stage_105=105&chk_stage_106=106&chk_stage_107=107&relative_survival_interval=5&hdn_sex=3&race=1&age_range=1&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_show_apc=on&advopt_display=1#resultsRegion0

Statistical Analysis

All statistical analyses performed using the statistical package for social sciences (SPSS) version 26 software tool. Quantitative data was summarized as medians and minimum-maximum (range) or mean +/- standard deviation (S.D), while qualitative data as percentages (%). Comparisons of group medians will be done using the Mann Whitney U test (z test) and Kruskal-Walli's test, while comparisons of % will be made by Chi-square test. The results will be considered significant if the *p*-value was less than or equal to 0.05.

Patients' survival is displayed by Kaplan-Meier survival curve; overall survival (OS) calculated

from the time of diagnosis till death, last follow up visit or end of study, progression free survival (PFS) calculated from the start of treatment till appearance of recurrence, death or the last follow up visit, and disease-free survival (DFS) will be calculated in all patients from the date of complete cure till date of recurrence, death from any cause or the last follow up.

RESULT

The study primarily concentrated on patients with non-epithelial ovarian tumors who received treatment at the Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, Faculty of Medicine, Mansoura University, Mansoura, Egypt, between January 2005 to June 2020. During this period a total of 505 patients presented with ovarian tumors. 382 patients were excluded per they didn't meet the inclusion criteria as having epithelial ovarian cancer or due to the presence of double malignancies or having an age less than 18 years as well as missing patients' files (n=123). Therefore, the study ultimately encompassed 56 patients.

Patients' demographic and clinic-pathological characteristics: Patients aged from 18 to 76 years with median 58 years, with 39.3% fell within the 35-50 years age range. Positive family cancer history was seen in 12.5%. Main complaints included pelvic mass (96.4%) and abdominal colic (62.5%). Tumor size is around 5 cm or more (96.4%), with 16 cm or more in 54 patients. ECOG performance status showed 55.4% PS 0.21.4% PS 1.23.2% PS 2-3. Most had no comorbidities (67.9%), 32.1% had diabetes, hypertension, ischemic heart disease or chronic kidney disease. 53.6% were premenopausal, and 46.4% postmenopausal. Most had unilateral ovarian tumors (91.1%). CA125 was elevated in 33.9%, however, AFP, ß-hCG, and LDH were elevated in 16.1%, 10.7%, and 8.9% of the patients, respectively. Approximately 10.7% had benign ovarian tumors and the rest (89.3%) had malignant tumors. Predominant tumors were ovarian sex cord tumors (64.3%), ovarian germ cell tumors (26.8%), and mesenchymal tumors (8.9%). Thirty-five patients had early-stage non-epithelial ovarian cancer (62.5%), while 26.8% had advanced disease at diagnosis.

Table 1. Ovarian patients' (n= 56) demographic and clinico-pathological characteristics

Characteristics	n (%)
Age (years)	
mean ± SD	45.57±16
median (min. – max.)	58 (18 - 76)
<35 years	13 (23.2%)
>50 years	21 (37.5%)
>50 years	21 (37.5%)
Family history	
Positive family history	7 (12.5%)
No	49 (87.5%)
Presenting symptoms	
Pelvic mass	54 (96.4%)
Abdominal colic	35 (62.5%)
Vaginal bleeding	17 (30.4%)
Abdominal distention	13 (23.2%)
Hormonal disturbance	3 (5.4%)
ECOG performance status	
PS 0	31 (55.4%)
PS 1	12 (21.4%)
PS 2	12 (21.4%)
PS 3	1 (1.8%)
Comorbidity presence	
Yes	18 (32.1%)
No	38 (67.9%)
Menopausal status	
Pre-menopausal	30 (53.6%)
Post-menopausal	26 (46.4%)
Site of primary ovarian tumor	
Bilateral disease	5 (8.9%)
Right ovary	31 (55.4%)
Left ovary	20 (35.7%)
Tumor marker (Unit)	
CA-125 (U/mL)	19 (33.9%)
AFP (ng/mL)	9 (16.1%)
LDH (U/L)	5 (8.9%)
B-hCG (mIU/mL)	6 (10.7%)
Histopathological type	
OGCTS	15 (26.8%)
Dysgerminoma	7 (46.7%)
Yolk sac tumor	3 (20%)
Mature cystic teratoma	1 (6.7%)
Immature cystic teratoma	3 (20%)
Monodermal teratoma	1 (6.7%)
OSCTS	36 (64.3%)
Granulosa cell tumor	26 (72.2%)
Sartoli leyding cell	3 (8.3%)
Fibrothecoma	3 (8.3%)
Fibroma	1 (2.8%)
Fibrosarcoma	3 (8.3%)
Mesenchymal tumor	5 (8.9%)
Mixed Mullerian tumor	3 (60%)
Stromal sarcoma	2 (40%)
Tumor size	
≤ 4cm	2 (3.6%)
≥5cm - ≤15cm	32 (57.1%)
≥16 cm	22 (39.3%)
Tumor type	
Benign	6 (10.7%)
Neoplastic	50 (89.3)
Tumor stages	
I	30 (60%)
II	5 (10%)
III	12 (24%)
IV	3 (6%)
Metastatic tumor	
Yes	8 (14.3%)
No	48 (85.7%)

Metastasis was reported in 14.3%, with peritoneal nodules (62.5%), lung and bone metastases in 2 cases, and soft tissue mass and abdominal lymph node metastasis in 1 patient (Table 1). In Table 2, treatment modalities analysis, where all 56 patients (100%) underwent surgery, 96.4% had upfront early debulking and 3.6% had interval debulking post-neoadjuvant chemotherapy. Fertility Sparing Surgery was performed in 50%, optimal debulking in 41.4%, non-optimal in 5.4%, and a ruptured capsule in 16.1%. Surgical debulking left no residual disease in 78.6% (44 patients); 12 patients had residual disease (R1 or R2), attributed to non-optimal debulking or tumor seeding after a ruptured capsule. Chemotherapy was administered to 55.4% of patients, with 67.7% receiving the BEP regimen and 9 patients receiving other regimens. Pathological responses in 12 patients with residual disease: 75% achieved complete response, 8.3% partial response, 8.3% stable disease, and 8.3% progressive disease. Neoadjuvant chemotherapy was given to 2 patients (6.4%), one achieving complete response with BEP, the other with stable disease on Paclitaxel/Carboplatin, proceeding to adjuvant therapy and interval debulking. Patients with stable or progressive disease underwent second-line chemotherapy. 8.9% developed recurrent disease one with locoregional recurrence, three with liver metastasis, one with lung metastasis, and another with bone metastasis.

Survival analysis in relation to the patients' (n=56) prognostic factors

After a median follow-up of 61 months (20 to 200 months), the study found a median overall survival (OAS) of 66 months (range: 22-201 months). The 5-year OAS rate was 94.6% for 53 patients. Median progression-free survival (PFS) was 66 months (range: 15-201 months), with a 5-year PFS rate of 85.7% for 48 patients. Among 44 completely treated patients, disease-free survival (DFS) was 83 months (range: 24-201 months), with a 5-year DFS rate of 93.2% for 41 patients (Figure 2) vs SEER Relative Survival Rates by Time Since Diagnosis, 2000-2019 Female addressing the Hispanic race, all ages, all stages (Figure 3).

Figure 2 depicted a significant difference in progression-free survival (PFS) between early-stage (I-II) and advanced-stage (III-IV) ovarian cancer, with a median PFS of 85 months vs. 53 months, respectively (*P*=0.001). The 5-year overall survival rate was 100% for early-stage and 80% for advanced-stage. OS and PFS outcomes highlighted disparities in between fertility sparing and optimal debulking surgery. Fertility sparing surgery demonstrated a 5-year PFS of 96.6%, while optimal debulking had 83.3% ($p < 0.001$). In terms of overall survival, fertility sparing surgery showed a 5-year rate of 100%, compared to 95.8% for optimal debulking ($p < 0.001$)

The impact of residual tumor after surgery on outcomes was statistically significant. Patients with no residual tumor (R0) had a superior PFS of 83 months, while R1 and R2 groups had lower PFS (52 and 50 months, respectively, p=0.007). The 5-year OAS was 97.7% for R0 and 100% for R1. The OAS for good performance status (PS 0-I) was 96.3% at 5 years, compared to 50% for poor performance status (PS II-III, $p < 0.001$) (Table 3).

Multivariate analysis in Table 4 identified timing of surgery (*p*=0.04) as the most significant factor affecting non-epithelial ovarian patients' (n=56) PFS. Stage showed marginal significance in influencing survival outcomes. For OS, no independent prognostic factors were identified, suggesting that the factors considered did not significantly impact OS.

DISCUSSION

Notably, non-epithelial ovarian tumors comprised approximately 15% of the cases in the study. This proportion is consistent with the findings of a larger, more extensive study that reported a prevalence of 10% in certain Asian, Central and South American countries (Matz et al., 2017).

The mean age of patients with non-epithelial ovarian cancer was 45.5±16 years, with a median age of 58 (range 18 - 76) years. Piatek et al. (2023) reported a median age was 28 (range 17–40 years), while Yang et al. (2018) reported a median age was 22 (range 8-37 years). In comparison to other studies, our results showed a higher median age.

Table 1. Ovarian patients studied (n=56) treatment modalities characteristics

Treatment analysis	n (%)
Surgical and/or Chemotherapy treatment	
Surgical only vs surgical with chemotherapy	25 (44.6%) vs 31 (55.4%)
Surgical timing	
Early vs Interval debulking	54 (96.4%) vs 2 (3.6%)
Type of debulking surgery	
Optimal debulking	24 (41.4%)
Fertility sparing surgery	29 (50%)
Non-Optimal debulking	3 (5.4%)
Residual after surgery	
R0 (no residual)	44 (78.6%)
R1 (microscopic)	6 (10.7%)
R2 (macroscopic)	6 (10.7%)
Rapture capsule	
Yes vs No	9 (16.1%) vs 47 (83.9%)
Chemotherapy treatment	
Adjuvant vs Neoadjuvant*	30 (96.8%) vs 2 (6.5%)
Tumor recurrence	
Yes vs No	5 (8.9%) vs 51 (91.1%)
Patients' status	
Censored vs Died	49 (87.5%) vs 7 (12.5%)

* One patient received adjuvant and neoadjuvant chemotherapy

Table 3. Median survival of significant univariate prognostic factors affecting PFS and OAS (months)

Prognostic factor	Progression free survival (months)		Overall survival (months)	
	Median (range)	*P* value, 95%CI (lower-upper)	Median (range)	*P* value, 95%CI (lower-upper)
Tumor stage				
Early stage + Benign	85 (24 – 201)	0.00, (0.00 – 0.052)	87 (60 - 201)	0.003, (0.00 – 0.084)
Advanced stage	53 (15 - 122)		63 (22 - 122)	
ECOG PS				
0– I	80 (15 - 201)	NS, (0.078 - 0.278)	84 (23 - 201)	<0.001, (0.000 – 0.053)
II – III	64 (22 - 122)		67 (22 - 122)	
Surgery type				
Optimal debulking	72 (15 - 201)	< 0.001, (0.00 – 0.52)	77 (46 - 201)	<0.001, (0.00 – 0.053)
Fertility sparing	86 (24 - 169)		88 (60 - 169)	
Palliative	21 (17 - 23)		35 (22 - 61)	
Residual tumor				
R0	83 (24 - 201)	0.007, (0.00 – 0.052)	85 (46 - 201)	0.005, (0.00 – 0.053)
R1	52 (15 - 73)		66 (60 - 73)	
R2	53 (17 - 122)		61 (22 - 122)	
Metastasis				
Yes	44 (15 -122)	<0.001, (0.00 – 0.052)	59 (22 – 122)	<0.001, (0.00 – 0.052)
No	82 (24 – 201)		84 (60 – 201)	

Statistics was performed

Table 4. Multivariate analysis of ovarian patients' (n=56) prognostic factors affecting OAS and PFS

Prognostic factor	OAS			PFS		
	P-value	95% CI		*P*-value	95% CI	
		Min	Max		Min	Max
ECOG PS	0.083	0.854	12.66	0.517	0.590	2.854
Comorbidities	0.287	0.367	29.721	NA	NA	NA
Tumor stage	0.143	0.386	726.01	0.061	0.841	1886
Surgery type	0.789	0.194	8.625	0.224	0.414	43.674
Surgical timing	NA	NA	NA	0.041	1.176	3609
Residual tumor	0.681	0.209	10.942	0.476	0.074	3.360
Metastasis	0.160	0.515	55.946	0.238	0.393	43.129

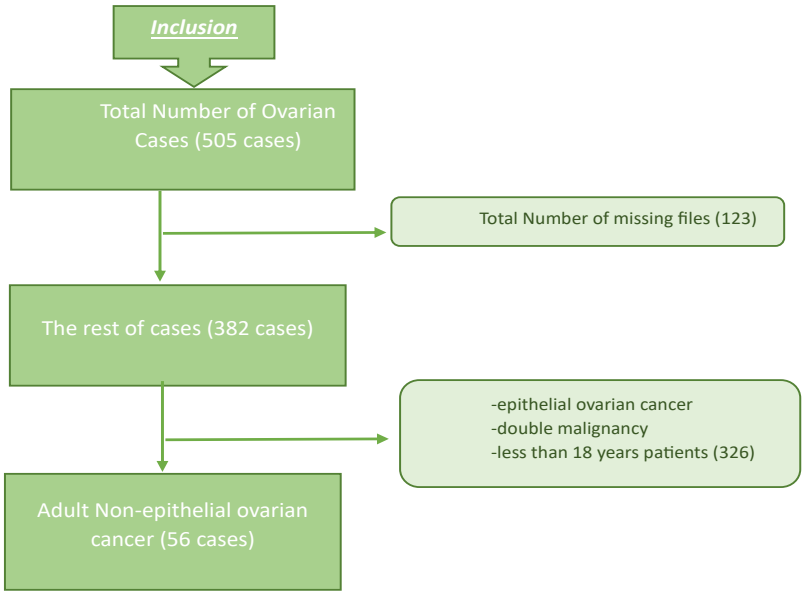

Figure 1. Number of Patients Enrolled in the study from January 2005 to December 2020

This difference can be attributed to the higher incidence of OSCTs in our study, in contrast to the higher incidence of OGCTs in the other mentioned studies. Precisely, the median age among OGCTs was 25 years and it was 48 years in OSCTs while, mesenchymal tumors were 67 years. This result is coping with Bennetsen et al. (2020) who reported median age of 36, 58, and 63 years for OGCTs, OSCTs, and mesenchymal tumor, respectively. Furthermore, our findings closely resemble those in a retrospective study by Seung-Hyuk Shim in 2012, who reported median ages of 26.5 years (range 12-35 years) for OGCTs and 42 years (range 7-57 years) for OSCTs.

Non-epithelial cancers, such as adult-type granulosa cell tumors and Sertoli-Leydig tumors, are frequently linked to non-BRCA1/2 gene mutations. Specifically, FOXL2 mutations are commonly associated with adult-type granulosa cell tumors, while DICER1 mutations are often found in Sertoli-Leydig tumors (Torre et al., 2018). A family history of cancer seems to exhibit an inverse correlation with the likelihood of developing germ cell tumors (GCTs). Furthermore, there is currently no identified genetic predisposition associated with the occurrence of mixed ovarian germ cell tumors (MOGCTs) (Brown et al., 2014). Notably, family history did not yield significant findings in this particular study.

The most symptomatic presentation in this study was pelvic mass in 96.4% of the cases and abdominal colics in 62.5%, this result is near to Bol et al. (2021) who reported pelvic mass in 97.1% and abdominal colic in 50% of patients. Also, the study by Boussios et al. (2016) noted the majority of patients presented with abdominal pain and a palpable pelvic-abdominal mass in 85% of OGCTs cases.

In the study conducted by Gomes et al. in (2020) 85% of the ovarian patients had unilateral ovarian tumor as their primary site. In contrast, the study under discussion here, 90% of the non-epithelial ovarian cancer patients studied exhibited a unilateral ovarian tumor as their primary site, which agreement with 91% reported by Zhang et al. in 2017. In the current study, it was found that 54% of the patients were in a pre-menopausal state. This approximates the findings in the study by Gomes et al. (2020) where pre-menopausal patients constituted 57% of the sample.

The majority of publications with substantial sample sizes have consistently shown that ovarian germ cell tumors (OGCT) have a higher prevalence. In a study with a sample size of n=1258 van der Hel et al. (2019), OGCTs accounted for 60% of cases, while (OSCTs) comprised about 27%, and sarcomas constituted 13%.

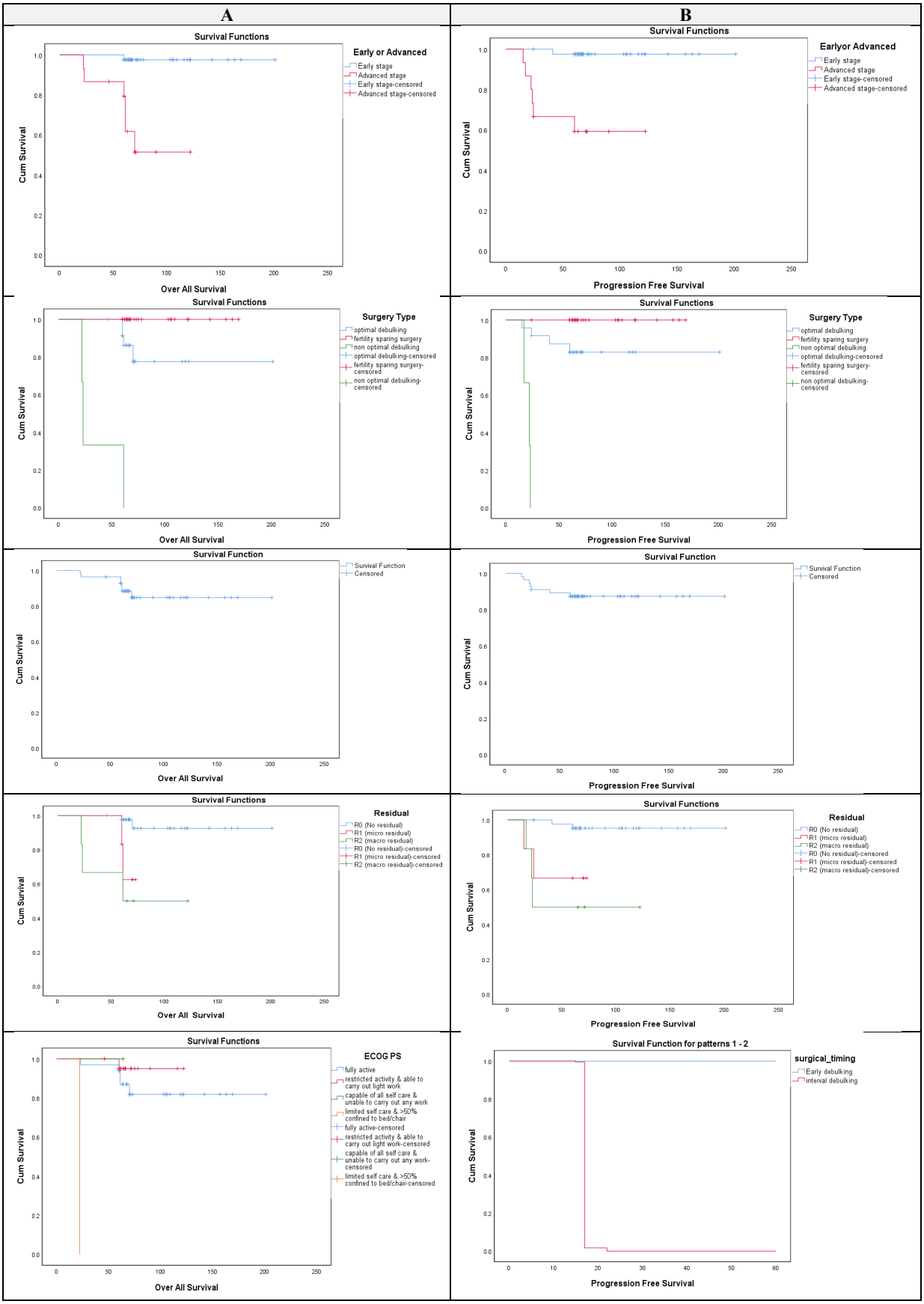

Figure 2. Kaplan-Meier Survival Curve; A: Overall survival, B: Progression Free Survival

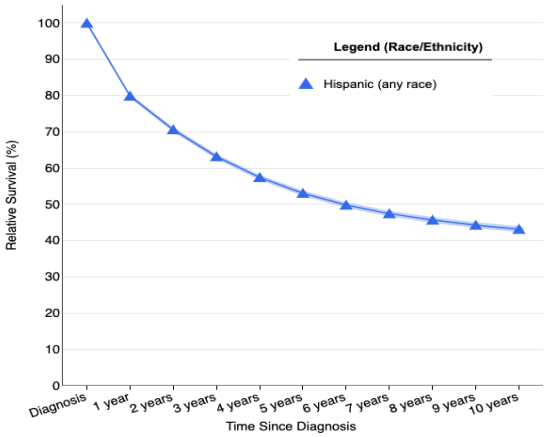

Figure 3. SEER Relative Survival Rates by Time Since Diagnosis, 2000-2019 Female addressing the Hispanic race, all ages, all stages. Accessed Dec. 18th, 2023. https://seer.cancer.gov/statistics-network/explorer/application.html?site=61&data_type=4&graph_type=6&compareBy=race&chk_race_6=6&hdn_sex=3&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_show_apc=on&advopt_display=

In another extensive study involving n=720 subjects Bennetsen et al. (2020), OGCTs made up around 50% of cases, OSCTs were approximately 38.6%, and mesenchymal tumors represented 11.5% of the cases. However, another study with a sample size of n=102 aligns with our current research. In the study by Bol et al. (2021), OSCTs were the predominant category, comprising 54% of cases, while OGCTs accounted for approximately 46%. These findings were consistent with the results of our study, where OSCTs were the most prevalent type at 64%, OGCTs accounted for 27%, and mesenchymal tumors had the lowest representation at around 10%.

The most prevalent histological subtype of ovarian sex cord-stromal tumors (OSCTs) was adult granulosa cells, constituting approximately 72% of cases in this study. This observation is in line with the study conducted by Gomes et al. (2020) who reported a similar distribution, with adult granulosa cell tumors representing around 71% of OSCT cases.

On the other hand, when it comes to ovarian germ cell tumors, the most common histological subtypes were dysgerminoma and yolk sac tumor, consistent at approximately 46% and 20%, respectively. This finding aligns with the results from a study by Bol et al. (2021) which also indicated a prevalence of dysgerminoma at 51% and yolk sac tumors at about 12.7%. Regarding the tumor stage at the time of diagnosis, in our study, approximately 70% of cases were in the early stages (I-II), with the remaining 30% classified as advanced stages (III-IV).

This distribution closely resembles the findings of an Iranian study, where early-stage cases comprised around 77% and the advanced-stage cases accounted for 27% of the total (Bol et al., 2021). We found in this study that 96% of all patients initially received surgical treatment, a result closely aligned with a study by Yang et al. (2018) which reported that 85% of their cases underwent primary surgical treatment.

Moreover, in our study, 50% of the patients underwent fertility preservation surgery (FPS) with no residual or residual ≤ 1 cm, 41% underwent optimal debulking surgery, and 5% underwent non-debulking surgery. These proportions are quite similar to the findings of a study by Bol et al. (2021), where 63% of cases underwent FPS, 32% had optimal debulking, and 4% had non-optimal debulking surgery. Among the 31 patients (55.4%) in this study who received chemotherapy, the majority received treatment with the BEP protocol (Bleomycin, Etoposide, and Cisplatin), either in the adjuvant or neoadjuvant setting 70.9%, and a complete response observed in 75% of cases. This percentage of patients receiving the BEP protocol is close to the findings of Zhang et al. (2017), who reported a rate of 82.9%.

However, in a more recent study by Piatek et al. (2023), involving a larger sample size of 146, a much higher percentage of 94% received the BEP protocol, with a remarkable 97.7% of those patients achieving a complete response to the treatment among the 86 patients (58.9%) who received chemotherapy. The median follow-up duration in our study was 61 months, a result closely resembling the findings of Bol et al. (2021), who reported a median follow-up of 59 months, and Piatek et al. (2023), where the follow-up was 63.3 months. In contrast, another study by Yang et al. (2018) reported an average (mean) follow-up of 72 months, which is similar to our study's 74 months.

In the current study, 8.9% of patients (5/56) experienced disease recurrence, with three of these recurrences occurring within the first 2 years of diagnosis and a mean interval to recurrence of 33 months. This recurrence rate aligns with the findings of Johansen et al. (2019), which reported a recurrence rate of 5% (4/73).

However, Yang et al. (2018) reported a higher recurrence rate of 11.5% (17/175) with a mean interval to recurrence of 37.8 months, and Piatek et al. (2023) found a relapse rate of 11.6% (17/146). In the study by Bol et al. (2021), 5.8% (6/102) of patients experienced relapse during the first 2 years. The impact of age as a prognostic factor remains a topic of controversy, as certain studies emphasize its significance while others do not Murugaesu et al. (2006). This study is consistent with research conducted in the Netherlands who found no association between age and survival outcomes (van der Hel et al., 2019).

The 5-year PFS in our study was 85.7% which closely matched the results of Yang et al. (2018) at 88.5%, Bol et al. (2021) at 94.3%, Piatek et al. (2023) at 91%, and Johansen et al. (2019) at 96%. In contrast, the 5-year OAS in our study was 94.6% consistent with the 93.9% reported by Yang et al. (2018), 98% by Johansen et al. (2019), and 99% by Bol et al. (2021). The increase in 5-year survival rates for ovarian cancer patients from 64-73% in 1989-1993 to 81-88% in 2010-2015 is attributed to advancements in medical care, as indicated by van der Hel et al. (2019). There was a statistically significant correlation between PFS (95%), OAS (100%), and early stage (p-value=0.001 and 0.003, respectively). This finding has been confirmed by several other studies, such as Bol et al. (2021) with a p-value of 0.01, van der Hel et al. (2019) with a p-value of 0.01, and Bennetsen et al. (2020), where the 5-year survival for localized disease was 88% (95% CI: 83, 93).

Regarding the type of surgery, the gold standard for surgical management of non-epithelial ovarian tumors is fertility-sparing surgery. In our study, the type of surgery was found to be statistically significant for both 5-year PFS and 5-year OAS (p-value <0.001), in line with the results of Karalok et al. (2019) (p-value=0.001).

Furthermore, the residual tumor after surgery in our study was statistically significant for 5-year PFS and 5-year OAS (p-value=0.007 and 0.005, respectively), a result consistent with the findings of Park et al. (2017) (p-value=0.001) and Chan et al. (2005) (p-value=0.002). The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was statistically significant for OS (p-value <0.001). Patients with a good performance status had a higher survival rate, which is consistent with the findings of Talukdar et al. (2014). However, further studies with larger sample sizes are needed to confirm the performance status as a prognostic factor.

However, multivariate analysis of significant prognostic factors on survival analysis showed that the timing of surgery was the most significant factor affecting Progression-Free Survival (PFS). This means that the timing of the surgical intervention had a strong impact on the length of time during which the disease did not progress. Additionally, the stage of the tumor at the time of diagnosis showed marginal significance in the multivariate analysis, indicating that it may have a moderate influence on survival outcomes.

In this study, treatment toxicities were observed, with hematological toxicities, gastrointestinal upset, and peripheral neuropathy being the most commonly encountered. Grade 1-2 toxicities were reported in 22 patients for anemia, 20 patients for leukopenia, and 24 patients for emesis. These findings align with the results of Talukdar et al. (2014), who reported grade 1-2 anemia in 20 cases, leukopenia in 20 cases, and emesis in 24 cases. Neutropenia was observed in 14 patients in our study, which is close to the incidence of neutropenia reported in the study by Pashankar and Frazier (2020), where it was present in 11 patients. Additionally, Derquin et al. (2020) reported 14 patients experiencing febrile neutropenia, further indicating the occurrence of neutropenic events in similar patient populations.

Strength in the current research resides in that it clarifies the significant impact of treatment on prognostic factors in favor for the survival

outcome in the rare non-epithelial ovarian cancer.

CONCLUSION

This study contributes valuable insights into the clinico-epidemiological aspects of non-epithelial ovarian cancer, emphasizing the importance of early diagnosis and tailored surgical approaches.

RECOMMENDATION

Further multi-centered research is needed to confirm the current study prognostic factors results. Management of treatment toxicities is a crucial consideration for patient's care and welfare to achieve "better health" SDG#3.

One of the main constraint/limitations in the current study was the sample size (N=56) for more significant results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION

Authors contributed equally to the study.

REFERENCES

Bennetsen, A.K.K., Ba, Rup, L., Aalborg, G.L. & Kjaer, S.K. 2020. Non-epithelial ovarian cancer in Denmark – Incidence and survival over nearly 40 years. Gynecologic Oncology, 157, 693-699.

Bol, I.S., Nakhaee, M., Shirinzadeh, L., Hossein Jafarian, A., Davachi, B., Zavari, T., Shirzadeh, F. & Yousefi, Z. 2021. Survival rate of non-epithelial ovarian tumors in Iran. Middle East Journal of Cancer, 12, 302-309.

BOUSSIOS, S., ZARKAVELIS, G., SERAJ, E., ZERDES, I., TATSI, K. & PENTHEROUDAKIS, G. 2016. Non-epithelial Ovarian Cancer: Elucidating Uncommon Gynaecological Malignancies. Anticancer Res, 36, 5031-5042.

Brown, J., Friedl, Er, M., Backes, F. J., Harter, P., O'connor, D.M., De La Motte Rouge, T., Lorusso, D., Maenpaa, J., Kim, J.W., Tenney, M.E. & Seckl, M.J. 2014. Gynecologic cancer intergroup (GCIG) consensus review for ovarian germ cell tumors. International Journal of Gynecological Cancer, 24, S48-S54.

CHAN, J. K., ZHANG, M., KALEB, V., LOIZZI, V., BENJAMIN, J., VASILEV, S., OSANN, K. & DISAIA, P. J. 2005. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--a multivariate analysis. Gynecologic oncology, 96, 204-9.

Derquin, F., Floquet, A., Hardy-Bessard, A.C., Edeline, J., Lotz, J.P., Alex, Re, J., Pautier, P., Angeles, M.A., Delanoy, N., Lefeuvre-Plesse, C., Cancel, M., Treilleux, I., Augereau, P., Lavoue, V., Kalbacher, E., Berton Rigaud, D., Selle, F., Nadeau, C., Gantzer, J., Joly, F., Guillemet, C., Pomel, C., Favier, L., Abdeddaim, C., Venat-Bouvet, L., Provansal, M., Fabbro, M., Kaminsky, M. C., Lortholary, A., Lecuru, F., Coquard, I. R. & De La Motte Rouge, T. 2020. Need for risk-adapted therapy for malignant ovarian germ cell tumors: A large multicenter analysis of germ cell tumors' patients from French TMRG network. Gynecologic Oncology, 158, 666-672.

Gomes, T.A., Campos, E.A., Yoshida, A., Sarian, L.O., Andrade, L. & Derchain, S.F. 2020. Preoperative Differentiation of Benign and Malignant Non-epithelial Ovarian Tumors: Clinical Features and Tumor Markers. Rev Bras Ginecol Obstet, 42, 555-561.

Johansen, G., Dahm-Kähler, P., Staf, C., Rådestad, A.F. & Rodriguez-Wallberg, K.A. 2019. Fertility-sparing surgery for treatment of non-epithelial ovarian cancer: Oncological and reproductive outcomes in a prospective nationwide population-based cohort study. Gynecologic Oncology.

Karalok, A., Comert, G. K., Kilic, C., Turkmen, O., Kilic, F., Basaran, D., Boyraz, G., Tekin Ö, M. & Turan, T. 2019. Cytoreductive surgery in advanced stage malignant ovarian germ cell tumors. J Gynecol Obstet Hum Reprod, 48, 461-466.

Liu Y, Xia J, Sun J and Zhao M. OCGene: a database of experimentally verified ovarian cancer-related genes with precomputed regulation information. Cell Death Dis. 2015; 6:e2036.

Matz, M., Coleman, M.P., Sant, M., Chirlaque, M.D., Visser, O., Gore, M., Allemani, C. & The, C.W.G. 2017. The histology of ovarian cancer: worldwide distribution and implications for international survival comparisons (CONCORD-2). Gynecol Oncol, 144, 405-413.

Murugaesu, N., Schmid, P., Dancey, G., Agarwal, R., Holden, L., Mcneish, I., Savage, P.M., Newlands, E.S., Rustin, G.J. & Seckl, M.J. 2006. Malignant ovarian germ cell tumors: identification of novel prognostic markers and long-term outcome after multimodality treatment. J Clin Oncol, 24, 4862-6.

Park, J.Y., Kim, D.Y., Suh, D.S., Kim, J.H., Kim, Y.M., Kim, Y.T. & Nam, J.H. 2017. Analysis of outcomes and prognostic factors after fertility-sparing surgery in malignant ovarian germ cell tumors. Gynecologic Oncology, 145, 513-518.

Pashankar, F. & Frazier, A.L. 2020. Re: A multicentre retrospective cohort study of ovarian germ cell tumours: Evidence for chemotherapy de-escalation and alignment of paediatric and adult practice. European Journal of Cancer, 130, 265-266.

Piatek, S., Szymusik, I., Sobiczewski, P., Michalski, W., Kowalska, M., Oltarzewski, M. & Bidzinski, M. 2023. Obstetric Results after Fertility-Sparing Management of Non-Epithelial Ovarian Cancer. Cancers (Basel), 15.

Seung-Hyuk Shim, M., Dae-Yeon Kim, MD, PHD, Shin-Wha Lee, MD, PHD, Jeong-Yeol Park, MD, PHD, Jong-Hyeok KIM, MD, PHD, Yong-Man Kim, MD, PHD, Young-Tak Kim, MD, PHD, & Joo-Hyun Nam, MD, PHD 2012. Laparoscopic Management of Early-Stage Malignant Nonepithelial Ovarian Tumors.

Talukdar, S., Kumar, S., Bhatla, N., Mathur, S., Thulkar, S. & Kumar, L. 2014. Neo-adjuvant chemotherapy in the treatment of advanced malignant germ cell tumors of ovary. Gynecologic Oncology, 132, 28-32.

Torre, L.A., Trabert, B., Desantis, C. E., Miller, K.D., Samimi, G., Runowicz, C.D., Gaudet, M.M., Jemal, A. & Siegel, R. L. 2018. Ovarian cancer statistics, 2018. CA Cancer J Clin, 68, 284-296.

VAN Der Hel, O.L., Timmermans, M., Van Altena, A.M., Kruitwagen, R., Slangen, B.F.M., Sonke, G.S., Van De Vijver, K.K. & Van Der Aa, M.A. 2019. Overview of non-epithelial ovarian tumours: Incidence and survival in the Netherlands, 1989-2015. Eur J Cancer, 118, 97-104.

Yang, B., Yu, Y., Chen, J., Zhang, Y., Yin, Y., Yu, N., Chen, G., Zhu, S., Huang, H., Yuan, Y., Ai, J., Wang, X. & Li, K. 2018. Possibility of women treated with fertility-sparing surgery for non-epithelial ovarian tumors to safely and successfully become pregnant—a Chinese retrospective cohort study among 148 cases. Frontiers of Medicine, 12, 509-517.

Zhang, N., Chen, R., Hua, K. & Zhang, Y. 2017. A retrospective study of reproductive outcomes after fertility-sparing surgery and postoperative adjuvant chemotherapy in malignant ovarian germ cell tumors and sex cord-stromal tumors. Journal of Ovarian Research, 10.

Brown, E., Stewart, M., Rye, T., Al-Nafussi, A., Williams, A.R., Bradburn, M., Smyth, J. & Gabra, H. 2004. Carcinosarcoma of the ovary: 19 years of prospective data from a single center. *Cancer,* 100**,** 2148-53.

Lang, J. D., Hendricks, W. P. D., Orlando, K. A., Yin, H., Kiefer, J., Ramos, P., Sharma, R., Pirrotte, P., Raupach, E. A., Sereduk, C., Tang, N., Liang, W. S., Washington, M., Facista, S. J., Zismann, V. L., Cousins, E. M., Major, M. B., Wang, Y., Karnezis, A. N., Sekulic, A., Hass, R., Vanderhyden, B. C., Nair, P., Weissman, B. E., Huntsman, D. G. & Trent, J. M. 2018. Ponatinib Shows Potent Antitumor Activity in Small Cell Carcinoma of the Ovary Hypercalcemic Type (SCCOHT) through Multikinase Inhibition. *Clin Cancer Res,* 24**,** 1932-1943.

Lawrie, T. A., Medeiros, L. R., Rosa, D. D., Da Rosa, M. I., Edelweiss, M. I., Stein, A. T., Zelmanowicz, A., Ethur, A. B. & Zanini, R. R. 2013. Laparoscopy versus laparotomy for FIGO stage I ovarian cancer. *Cochrane Database Syst Rev***,** Cd005344.

Lucidi, A., Chiantera, V., Gallotta, V., Ercoli, A., Scambia, G. & Fagotti, A. 2017. Role of robotic surgery in ovarian malignancy. *Best Pract Res Clin Obstet Gynaecol,* 45**,** 74-82.

Miller, B. E., Barron, B. A., Wan, J. Y., Delmore, J. E., Silva, E. G. & Gershenson, D. M. 1997. Prognostic factors in adult granulosa cell tumor of the ovary. *Cancer,* 79**,** 1951-5.

Oken MM, C. R., Tormey DC, Horton J, Davis TE, Mcfadden ET, et al. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group (ECOG). *The American Journal of Clinical Oncology*.

PARK, H. J., KIM, D. W., YIM, G. W., NAM, E. J., KIM, S. & KIM, Y. T. 2013. Staging laparoscopy for the management of early-stage ovarian cancer: a metaanalysis. *Am J Obstet Gynecol,* 209**,** 58.e1-8.

Ray-Coquard, I., Morice, P., Lorusso, D., Prat, J., Oaknin, A., Pautier, P., Colombo, N. & Committee, E. G. 2018. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol,* 29**,** iv1-iv18.

Thomakos, N., Malakasis, A., Machairiotis, N., Zarogoulidis, P. & Rodolakis, A. 2018. Fertility Sparing Management in Non-Epithelial Ovarian Cancer. Which Patients, What Procedure and What Outcome? *J Cancer,* 9**,** 4659-4664.

Zhang, N., Chen, R., Hua, K. & Zhang, Y. 2017. A retrospective study of reproductive outcomes after fertility-sparing surgery and postoperative adjuvant chemotherapy in malignant ovarian germ cell tumors and sex cord-stromal tumors. *Journal of Ovarian Research,* 10.