

Non-Epithelial Ovarian Cancer, an Experience From Qatar

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Abstract

Background: Nonepithelial Ovarian cancers constitute about 10 % of all ovarian cancers. They are divided into Sex-cord stromal tumours (SCST) and Germ cell tumours (GCT). The Aim is to report the experience at National Centre for Cancer Care and Research (NCCCR) in Qatar.

Method: This is a retrospective study reviewing records of all patients over 7 years who presented with a histopathologically diagnosed ovarian SCST and GCT at NCCCR between January 2010 and December 2016.

Results: 25 women with Non-Epithelial Ovarian Tumours were identified. 13 women were diagnosed with Ovarian SCST. Median age at presentation was 43 years (Range 16-58). 12 patients had stage I and one patient had Stage III. Four patients had recurrence. The 5 years Overall Survival (OS) was 100% and the 5 years Event Free Survival (EFS) was 69% with P value of 0.02. GCT was diagnosed in 12 women. The median age at presentation was 24 years. (Range 16 – 44). Seven patients (59 %) had teratoma, four patients (33 %) had Dysgerminoma and one patient had Yolk sac tumour (8 %). There was one recurrence. 5 years OS was 100 % and 5 years EFS was 83 % with P value of 0.14.

Conclusions: Non-Epithelial ovarian tumours are diagnosed relatively at an early stage and have very good prognosis even if they recur. Survival in our study was excellent with all patients alive and disease free at last follow up. For ovarian SCST, we recommend Complete Surgery (TAH + BSO) particularly if high grade, Stage IC and above or completed childbearing to minimize recurrence. Fertility sparing surgery is appropriate for all patients with Stage I Ovarian GCT and most of the patients with Stage II disease who desire fertility preservation.

Background

Nonepithelial ovarian cancers constitute about 10 % of all ovarian cancers. They are divided into sex-cord stromal tumours (SCST) or germ cell tumours (GCT). Both these groups are further subclassified based on histology. They differ markedly from epithelial ovarian cancer in prognosis and treatment (1).

SCST comprise 5-8 % of all ovarian tumours (2,3). The majority are Granulosa cell tumours and the remainder of this group consist of Sertoli Leydig cell tumour, Fibroma – Thecoma and steroid cell (3). SCST usually present at a younger age, are generally early stage at diagnosis, grow slowly and have an overall favourable prognosis (3).

Surgical Resection i.e. Total Abdominal Hysterectomy and Bilateral Salpingo – Oophorectomy (TAH+BSO) is the mainstay of treatment. For younger patients with early stage disease who desire fertility preservation, conservative surgical approach with Unilateral Salpingo-Oophorectomy has been suggested as a treatment option. Adjuvant chemotherapy is not generally administered after complete surgical resection (4).

Ovarian Germ cell tumours (GCT) comprise approximately 5 % of all ovarian tumours. They occur primarily in adolescent girls and young women between 10 and 30 years of age and represent 70 percent of ovarian neoplasms in this age group (5). Fertility- sparing surgery is the cornerstone for most patients. OGCTs are broadly classified into dysgerminomas and non-dysgerminomas which include yolk sac tumours, immature teratomas, mixed germ cell tumours and non-gestational choriocarcinomas. Patients with stage I dysgerminomas and stage I, grade 1 immature teratomas can be treated with surgery alone. BEP (bleomycin, etoposide, and cisplatin) is the most widely used regimen with most data supporting three to four cycles (6,7) .

Due to the rare nature of these tumours, very limited data has been reported in the literature. To our knowledge, this is the first study in the Arabian Gulf to report the clinicopathologic features, treatments and outcomes of Ovarian SCSTs and GCTs.

This study presents retrospective data from 25 patients with histopathologically diagnosed Sex cord stromal tumours and Germ cell Tumours of ovary seen at the only tertiary cancer centre, National Centre for Cancer Care and Research (NCCCR) in Doha, Qatar over a 7-year period.

Methods

We reviewed the records of all patients with histopathologically established ovarian SCST and GCT treated at NCCCR Doha, Qatar between January 2010 and December 2016. The study was approved by Research Ethics Committee of NCCCR and Medical Research Centre of Hamad Medical Corporation. All available medical records of the patients available in paper file and Cerner, including outpatient and inpatient visits were reviewed. Clinical data of patients including age, presenting complaints, tumour markers, imaging studies, histopathology, stage at diagnosis, treatment received, disease relapse and condition at last visit was extracted using a standardized data extraction form. Data was entered in Microsoft Excel (Version 2010) and was analysed using STATA SE version 11.0.

Descriptive statistics were calculated for all patients. Survival analyses were done using the Kaplan-Meier method. A two-sided p-value less than 0.05 were considered statistically significant.

Overall Survival (OS) was defined as the duration in months from the date of diagnosis to death or loss of follow up. Event free survival (EFS) was defined as the duration in months from the start of treatment to documented recurrence or progression.

Results

A Total of 25 women were diagnosed with Non-Epithelial Ovarian Tumours. Around two-thirds of them were Arabs and the rest were Asian and one was African (Fig.1). The Mean follow up period for the entire study sample was 93.2 months (40 – 123).

13 women were identified with ovarian sex cord stromal cell tumours. 12 of these patients had granulosa cell tumour and one had steroid cell tumour. None of the patients had Sertoli-Leydig cell tumour.

The Median age at presentation was 43 years (Range 16-58).

Nine patients were from Arab countries mainly from Qatar and Egypt, three were from Asian countries mainly Philippines and one was from Nigeria.

12 patients (92 %) had stage I and one patient. (8 %) had Stage III. None of the patient had Stage II and IV.

Eight patients had TAH + BSO including the one with Stage III. Five patients had conservative surgery i.e. Unilateral Salpingo-oophorectomy without hysterectomy. Two patients received Adjuvant chemotherapy. (Table 1)

Four patients had recurrence.

All the patients were alive and disease free at last follow-up. One patient travelled back to her home country. The 5 years overall OS was 100% and the 5 years EFS was 69% with P value of 0.02 as shown in figure 2.

Table 1: Clinical Characteristics of Sex Cord Stromal Tumors

Variables	N	%
Pathological diagnosis		
Granulosa cell Tumor	12	92%
Steroid cell Tumor of Ovary	1	8%
Stage		
Stage IA	10	77%
Stage IC	2	15
Stage III	1	8%
Treatment modalities		
Surgery	11	84%
Surgery + chemo	2	16%
Type of Surgery		
TAH+BSO	8	62%
U/L Salpingo-oophorectomy	5	38%

	Median	1-year survival	5-year survival	P-value
Overall survival	Not reached	100%	100%	0.02
Event free survival	118 months	94%	69%	

Germ cell tumour (GCT) was diagnosed in 12 women.

The median age at presentation was 24 years. (Range 16 – 44). 75% of patients (9 patients) were below 30 years of age.

Seven patients (59 %) had teratoma. Four patients (33 %) had Dysgerminoma. One patient had Yolk sac tumour (8 %).

Nine patients (75 %) were diagnosed early at Stage I, TWO patients in Stage II and one patient had Stage IV disease. Almost all Patients had Unilateral Ovariectomy except one patient with Stage IV disease who received chemotherapy alone. (Table 2)

Following surgery, six patients with Stage I Dysgerminoma and Stage I Grade 1 Immature Teratoma were put under surveillance.

Chemotherapy was administered in six patients (50 %). BEP chemotherapy was used in all the patients. There was one recurrence in the retroperitoneal LNs in patient with Stage II disease with dysgerminoma ,she was treated with Surgery and Chemotherapy and is in remission.

All patients were alive and disease free at last follow-up. 5 years OS was 100 % and 5 years EFS was 83 % with P value of 0.14 as shown in Fig (3)

Table 2: Clinical characteristics of Germ Cell Tumours

Variables	N
Pathological diagnosis	
Dysgerminoma	4
Teratoma of Ovary	7
Ovarian Yolk sac Tumor	1
Stage	
Stage IA	6
Stage IC	3
Stage II	2
Stage IV	1
Treatment modalities	
Surgery (oophorectomy)	6
Surgery+ chemo	5
Chemotherapy	1

	Median	1-year survival	5-year survival	P-value
Overall survival	Not reached	100%	100%	0.14
Event free survival	Not reached	91%	83%	

Discussion

Non-Epithelial Ovarian tumours are relatively uncommon constituting around 10% of all ovarian cancers. Most studies are retrospective involving small number of patients. There is no study to our knowledge that has reported experience with Non-Epithelial Ovarian cancers in the Arabian Gulf. This study presents 7 years of retrospective data from 2010-2016 of patients diagnosed with SCST and GCT in the only tertiary cancer centre (NCCCR) in Doha, Qatar. Out of 25 patients diagnosed with Non-Epithelial Ovarian cancers 13 were SCST and 12 were GCTs.

In the SCST, most of them had granulosa cell tumours, were aged 16–58 years. 8 (62%) of our patients presented before 50 years of age.

12 patients (92 %) presented in stage-I, and only 1 in stage-III. With regards to treatment, majority were treated with surgery alone involving total abdominal hysterectomy with bilateral or unilateral salpingo-

oophorectomy. Around a third of the patients underwent fertility-sparing surgery. Granulosa cell tumours are the most frequent type of Ovarian SCST in almost all the studies, followed by Sertoli Leydig cell tumour (SLCT) (8).

In our study too, almost all patients had Granulosa Cell Tumour apart from 1 patient who was diagnosed with steroid cell tumour. We did not find any patient with Sertoli Leydig cell tumour probably because of a small sample size. Studies show varied results of the effect of age on prognosis of SCST. Studies by Stenwing et al and Fox et al show older patients had decreased survival (9,10). In the study led by Bjorkholm et al, there was no significant impact of age on survival (11). In our study too, we did not find any association of age with survival. Four patients had recurrence in our study. There were 3 Egyptians in the study and all of them had recurrence. The fourth lady who had recurrence was Qatari. 2 had Stage 1A disease. Other 2 had Stage 1C disease and one of them had Grade 3 disease. 2 women's age was 58 years. Another important predictor of survival shown in many studies is tumour stage; The higher the tumour stage, lesser the survival (12,13).

In Our study almost all the patients were Stage I at diagnosis and only one patient was Stage III. All the patients are alive and disease free at last follow-up. One patient travelled back to her home country.

The good results in our study are probably because 92 % of patients were Stage I at diagnosis.

In the treatment of young patients who desire to become pregnant, fertility sparing surgery is an important factor. Some studies suggest that fertility- sparing surgery might be offered to young patients (14,15). In our study, out of five patients who underwent conservative surgery, two (40 %) had recurrence. two women were given chemotherapy following surgery.

In our study with GCTs, the median age was 23 years (range 15–45 years), which was higher than that reported by Talukdar et al (16) , and similar to the study reported by M.M. Saber et al (17). In our study, teratomas were the most common pathologies followed by dysgerminomas which align with the European data showing that teratomas as the most common GCTs (18).

In our study, fertility preservation surgery was done for all the patients except one patient with Stage IV disease who received chemotherapy alone. This is in line with the published guidelines where unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is considered the adequate surgical treatment for patients with GCTs (19,20).

Six patients were kept under surveillance (4 had teratoma and 2 had dysgerminoma). five were Stage IA and one patient was stage II as she refused to receive chemo. Unfortunately, she was the only one in the entire study that had relapse after 10 months in the retroperitoneal LNs and achieved complete response– CR - after surgery and chemotherapy (BEP protocol).

This explains the importance of receiving Adjuvant chemotherapy in patients with Stage II or higher and those with Stage IA Immature Teratoma Grade 2/3. Also, reflects the good prognosis of this disease as there was only one Relapse in our cohort.

Chemotherapy was administered in six patients; Three patients with Teratoma, two with Dysgerminoma and one with Yolk sac tumour of ovary. (4 patients had Stage I, 1 had Stage II and 1 had Stage IV), BEP regimen was administered in all the cases. Almost all patients received three cycles and was well tolerated except one patient with Stage IV disease received two cycles BEP followed by four cycles Paclitaxel + Carboplatin because of hematologic toxicity. None had pulmonary toxicity. All patients were maintained in complete remission after finishing chemotherapy.

The patient with Stage IV disease on follow up was found to have Mediastinal mass which on biopsy was proved to be T cell Lymphoblastic Leukaemia. She received chemotherapy and is in remission. All patients were alive at last follow up.

Rogers et al reported better survival with early compared to late stage disease (21). There was no OS difference in our study between early and late stage disease, which was similar to Talukdar et al. (16). These differences might be explained by the smaller number of cases in the current study. In our study, the median OS was not reached reflecting the good prognosis of GCTs. This study is the one of the very few to report on Non-Epithelial Ovarian Tumours in the Middle East.

Our study has few limitations. First, this is a retrospective study because of the slow growing and indolent nature of these rare tumours. However, such a rare disease is best followed in a retrospective setting as prospective collection of enough number of patients will take long time and need the collaboration of many centres. Second, the no. of patients is less. Despite these limitations, this is the only study that reports clinical outcomes of patients with nonepithelial ovarian cancers from an Arabian Gulf country.

Another strength of this study is the relatively long follow up period with more than 90 % of the patients being followed up for longer than 5 years. Also, patients from various nationalities are part of the study since Qatar being a country with large Expat population.

Conclusion

Non-Epithelial Ovarian tumours are diagnosed relatively at an early stage and have very good prognosis even if they recur. Survival in our study was excellent with all patients alive and disease free at last follow up. For ovarian SCST, we recommend complete surgery (TAH + BSO) particularly if high grade, Stage IC and above or completed childbearing to minimize recurrence. Fertility sparing surgery is appropriate for all patients with Stage I ovarian GCT and most of the patients with Stage II disease who desire fertility preservation.

Abbreviations

1. Sex-cord stromal tumours (SCST)
2. Germ cell tumours (GCT)

3. National Centre for Cancer Care and Research (NCCCR)
4. Overall Survival (OS)
5. Event Free Survival (EFS)
6. Total Abdominal Hysterectomy and Bilateral Salpingo – Oophorectomy
7. BEP (Bleomycin, Etoposide, and Cisplatin)

Declarations

- Ethics approval and consent to participate

Informed consent was waived and “consent waiver” was obtained from the Ethics Committee of Medical Research Centre at Hamad Medical Corporation. The Informed consent was waived as it is a Retrospective study and anonymity of the participants was respected.

All the experiment protocol for involving humans was in accordance with the Declaration of Helsinki in the manuscript.

This manuscript was approved by the Medical Research Centre at Hamad Medical Corporation under Reference No. RP 17044/17

- Consent for publication

Not Applicable

- Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests

- Funding

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- Author Contributions

AM conceived and designed the work, did literature review , collected and analysed the data and wrote the paper, NO did literature review and collected the data, critically revised the paper , HM conceived and designed the idea and revised the manuscript , HG performed the analysis , AA, CJ and AK contributed to data collection , MY critically revised the paper. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Figures

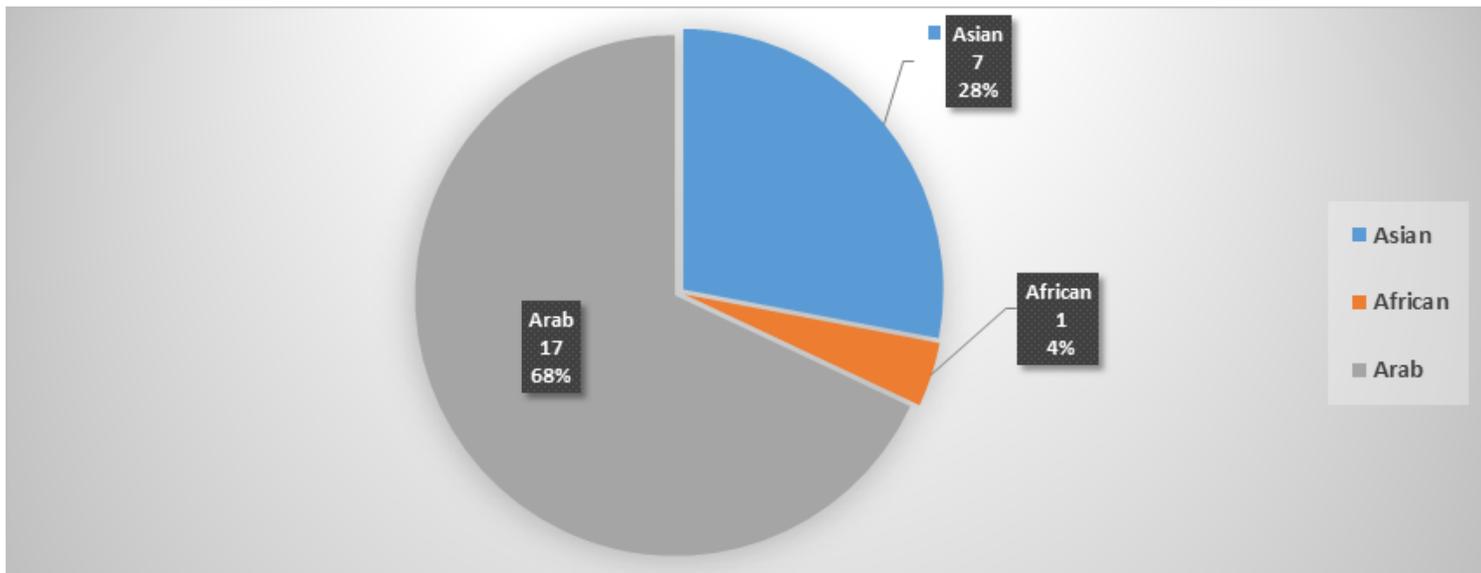


Figure 1

ETHNICITY OF PATIENTS WITH NON EPITHELIAL OVARIAN CANCER

Event-free survival (EFS) and overall survival (OS)

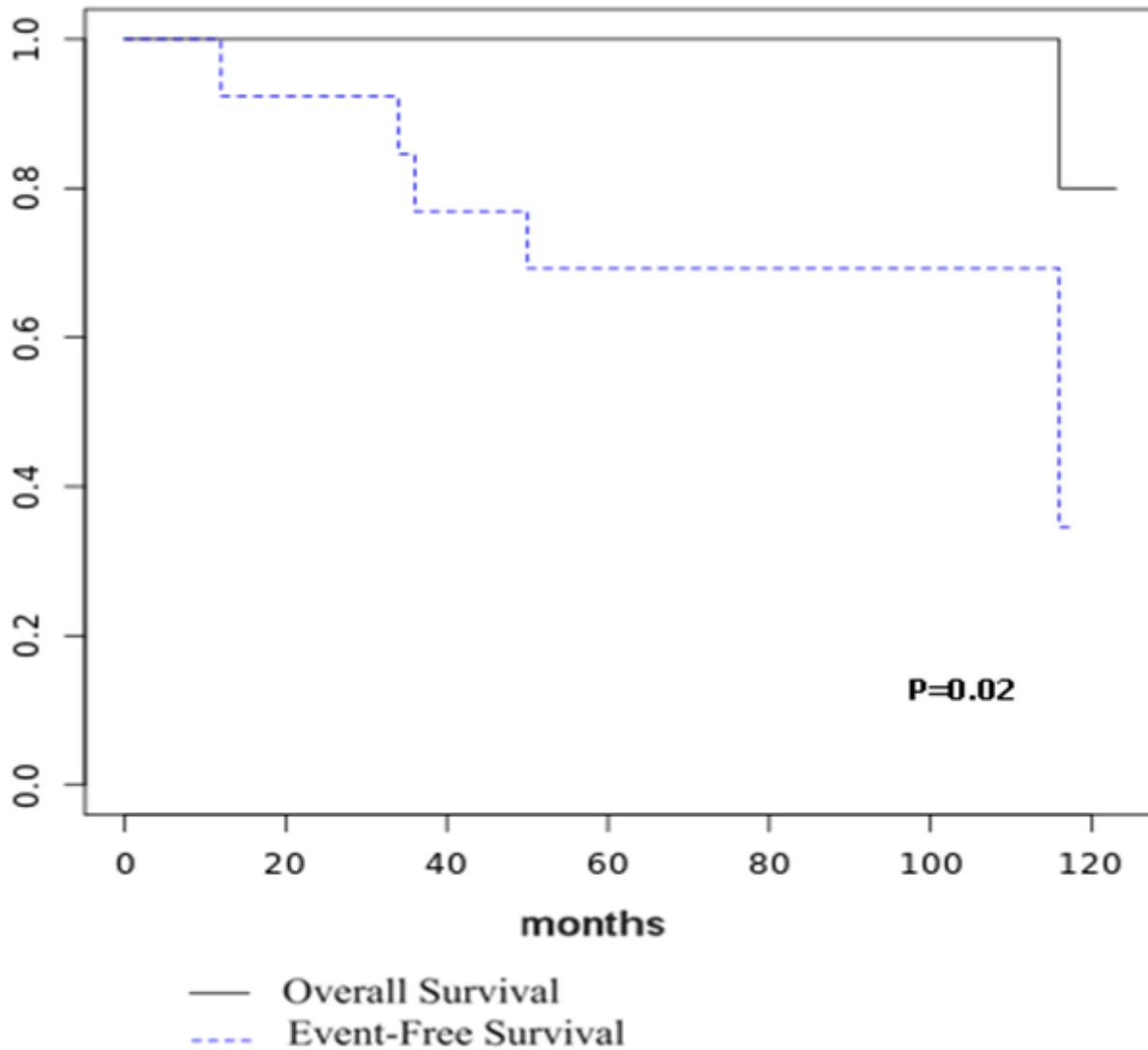


Figure 2

Kaplan Meir curve for Sex cord stromal tumors OS & EFS

Event-free survival (EFS) and overall survival (OS)

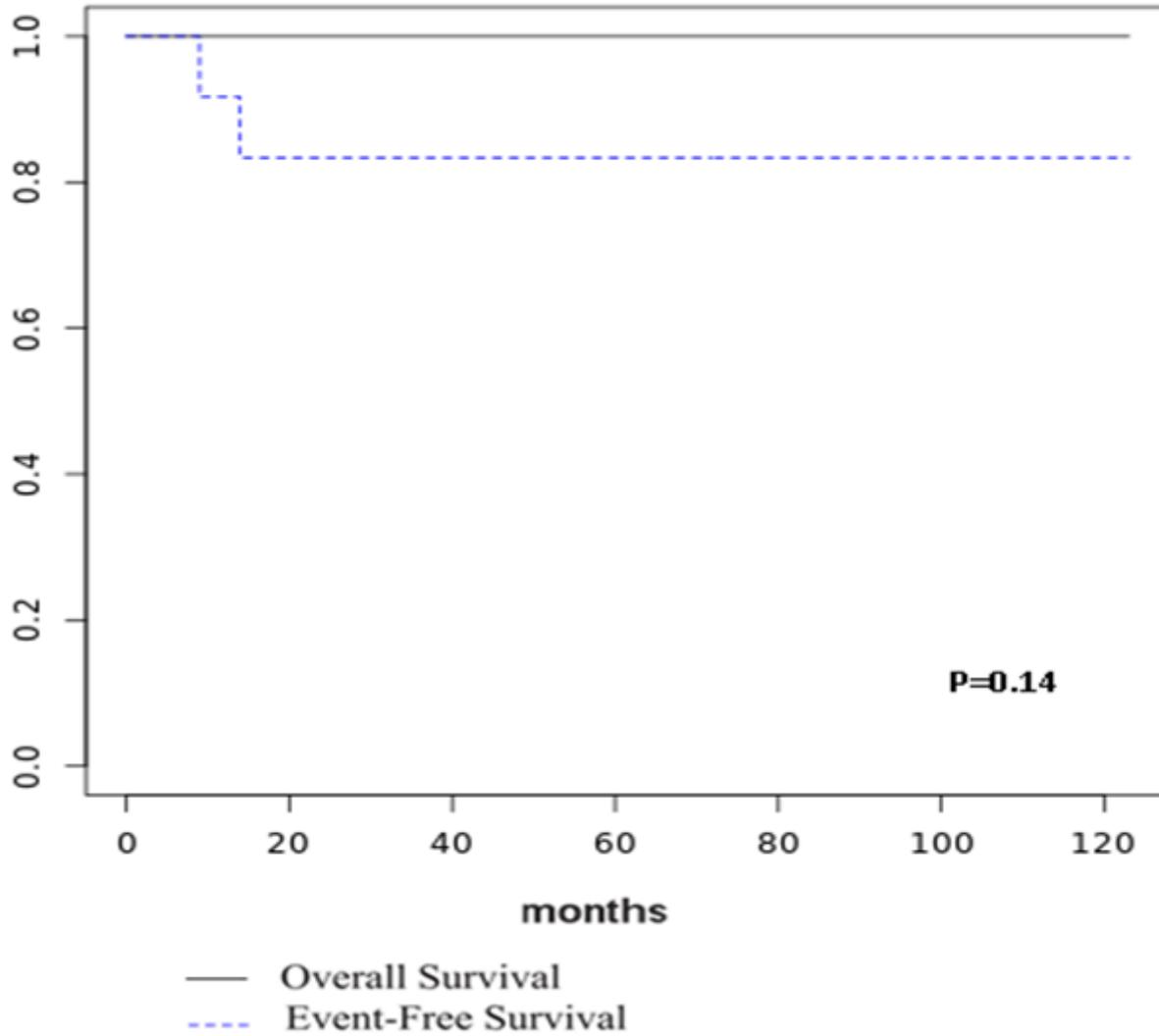


Figure 3

Kaplan Meir curve for germ cell tumours OS & EFS