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CLINICAL-PATHOLOGICAL PRESENTATION, TREATMENT AND OUTCOMES OF OVARIAN CANCER CASES AT MOI TEACHING AND REFERRAL HOSPITAL (MTRH), ELDORET

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Keywords: Ovarian Cancer; Histological Types; Treatment, Survival

ABSTRACT

Introduction: Ovarian cancer is the third most frequent cause of death amongst gynecological cancers both locally and globally. It presents with vague nonspecific symptoms and is histologically heterogeneous. Ovarian cancer management is primarily surgical followed by adjuvant chemotherapy depending on the histological type and the surgical stage.

Objectives: To determine the clinical-pathological presentation, treatment and outcomes of ovarian cancer patients at Moi Teaching and Referral Hospital (MTRH), Eldoret.

Methods: This was a retrospective chart review of ovarian cancer patients managed between January 2010 and August 2017 at MTRH. Data were analyzed using STATA version 15. Survival trends were generated using Kaplan Meier method.

Results: A total of 124 medical charts of patients with ovarian cancer were retrieved, 29 had incomplete data and were excluded, and 95 were evaluable and included in this review. Over half, (63%) presented in stage 3 and 4 though there was no significant association between histology and stage of disease [X2(6) =4.72, p=0.58]. The median age at diagnosis was 47 years with 55-80 years being the modal age group (36%). Majority (57%) were married and 83.9% were unemployed. Only 66% had documented histopathology, with Epithelial Ovarian Cancer (EOC) being most common (70%), [serous (50%) and mucinous (11.4%)]. Sex cord stromal tumors 11%. Germ cell tumors amounted to 11% (dygerminomas 50%and Yolk sac tumors (25%) Bivariate analysis revealed significant association only between histology and parity [X2 (6) = 28.8, p<0.001].

Those reviewed contributed a total of 138.2 person-years to the study and 11(12%) died, giving a disease-specific mortality rate of 79.6 per 1,000 person years (95% CI: 44.1-143.8). Mortality was highest among those with epithelial histology 109 (95% CI: 48.8-241.9) per 1,000 person years and those who had neoadjuvant chemotherapy then surgery as a treatment option, 373.1 (95% CI: 93.3-1491.8) per 1,000 person years. Those who underwent upfront surgery followed by adjuvant chemotherapy and sex cord stromal cancer had higher survival probability.

Conclusion: Ovarian cancer at MTRH is diagnosed at advanced stages III and IV of disease and has a lower median age at presentation. EOC is the commonest histological type and serous subtype is the most lethal. Mortality was highest among those with EOC and those who underwent neoadjuvant chemotherapy. Granulosa cell tumor is the only sex cord stromal type reported in our setting and it exhibited a higher survival probability. Germ cell tumors were mainly found in nulliparous women.

INTRODUCTION

Ovarian cancer accounts for 4% of all cancers occurring in women, with higher incidence rates in the United States and Northern Europe and lower rates in Africa and Asia. It is the third most frequent cause of death among gynecological cancers both locally and worldwide (Seidman et al., 2004) Approximately 85% of cases occur after age 50, and 80% to 85% of cancers are epithelial in origin. Traditionally, serous tumors are the most common, present at an advanced stage, and have the poorest outcome. In the reproductive age group, however, germ-cell tumors, sex-cord tumors, mucinous and endometrioid tumors are more common (Seidman et al., 2004, Cheserem et al., 2013)

In Kenya, most cases of ovarian cancer are diagnosed at advanced stages III and IV of disease (Cheserem et al., 2013). Advanced age has been postulated as a major risk factor for developing ovarian cancer especially the epithelial type. Locally, at The Kenyatta National Hospital in Nairobi, more than half of the women with ovarian cancer are diagnosed in the advanced stages of the disease and overall poor prognosis with a survival at 2 years from diagnosis being less than 60%. Specifically, majority (75%) of ovarian cancer cases are diagnosed at stage III and IV of disease (Cheserem et al., 2013).

Primary debulking surgery followed by adjuvant platinum-based chemotherapy has long been the standard of care for ovarian cancer. Neoadjuvant chemotherapy followed by interval debulking surgery has recently emerged as an alternative strategy. Large randomized trials have found non-inferior survival for neoadjuvant chemotherapy compared with upfront cytoreductive surgery (Kehoe et al., 2015). Staging laparotomy is performed and includes total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic, and para-aortic lymph node sampling (up to renal vein level), peritoneal sampling (multiple peritoneal biopsies and peritoneal cytology) and omentectomy (Atif et al., 2016).

We conducted this study to determine the clinical-pathological presentation, treatment and outcomes of ovarian cancer cases at MTRH, providing an institutional experience.

METHODOLOGY:

Study design: This was a retrospective study

Study setting: This study was carried out in the Outpatient Gynecological Oncology Unit at Chandaria Cancer and Chronic Diseases Management Centre, Moi Teaching and Referral Hospital (MTRH), Eldoret. The hospital is a public referral and teaching hospital located in Eldoret Town, Western Kenya offering specialized services for women with gynecological malignancies including ovarian cancer. The hospital also receives referrals of patients with histologically confirmed ovarian cancer having already undergone surgery. Following cytoreductive surgery and histologic diagnosis, these patients receive chemotherapy depending on the histological subtype. During follow up, the patients' details are recorded in manual ovarian cancer encounter forms then transcribed into the electronic filing system for all cancer cases presenting at the unit. At registration, the patients' and kin's address and telephone contacts are obtained to reduce loss-to-follow-up. It is during such follow up calls coordinated by the Clinical Research Assistant that some are determined to be deceased, at which point the patients' records are updated accordingly.

Study population: Records of all patients with diagnosis of cancer of the ovary at the MTRH between January 2010 and August 2017 were retrieved by the primary investigator and research assistants.

Data collection, management and Analysis: Using an extraction form, the following data were retrieved: age of patient, residence, histological diagnosis, stage at presentation, treatment and treatment outcome, survival and follow up. Statistical analysis was carried out using STATA Version 15. Summary statistics were reported with respect to the outcome (dead/alive) for all patient demographic, histological and treatment factors. The median and inter-quartile range were reported for age. All independent variables were also stratified by outcome and absolute counts and proportions were reported. Further, associations between the various explanatory factors and outcome were assessed using Chi Square test. Survival trends were generated using Kaplan Meier method.

Ethics: Ethical clearance was obtained from the Research and Ethical Committee of Moi University/MTRH

RESULTS

A total of 124 medical charts of patients with ovarian cancer were retrieved, 29 had incomplete data and were excluded and 95 were evaluable and included in this review. The socio-demographic characteristics of the study population are shown in Table 1. The median age at diagnosis was 47 years (7–82 years). The modal age group was 55-80 years (35, 36%). Half of these women were married (54, 57%), and unemployed (73, 83.9%). Majority of the patients (82.8%) were referrals from other hospitals.

Table 1: Socio-demographic characteristics of the study population

Variable	N	n (n/N%)
Age	95	
<20		10(10.53)
21-30		8(8.42)
31-40		14(14.74)
41-50		18(18.95)
51-60		19(20)
61-70		21(22.11)
71+		5(5.26)
Marital status	94	
Single		26(27.7)
Married/Living together		54(57.4)
Separated/Widowed		14(14.9)
Employment	87	
Employed		14(16.1)
Not employed		73(83.9)
Parity	79	
0		18(22.8)
1-4		28(35.4)
5+		33(41.8)
Education level	94	
Primary		8(8.5)
Secondary		12(12.8)
College/Tertiary		10(10.6)
None		11(11.7)
Not indicated		53(56.4)
Referral status	93	
Not referred		16(17.2)
Referred		77(82.8)

Of the 95 patients, 63 (66%) had a documented histological diagnosis in the patients chart. Patients with epithelial ovarian tumours constituted 69.8%, sex cord/stromal 11.1%, germ cell 11.1% and other histologies 7.9% (Table 2). Upon stratification, of the epithelial group, serous, mucinous, endometrioid, unspecified, and others made up 22 (50%), 5 (11.4%), 3 (6.8%), 6(13.6%), and 8(18.2%) respectively. The only documented sex cord stromal tumor subtype was granulosa cell tumor. Dysgerminomas, yolk sac/endodermal sinus tumors and immature teratomas were observed in 57.1%, 28.6% and 14.3% respectively among those with germ cell tumors.

Table 2: Histopathological diagnosis of the study population (NT=63)

Histopathological diagnosis and subtypes	nf, (nf/ NH%)	NH,(nH/ NT%)
Epithelial		44 (69.8)
Serous	22 (50)	
Mucinous	5 (11.4)	
Endometrioid	3 (6.8)	
Unspecified Carcinoma	6 (13.6)	
Other	8 (18.2)	
Sex cord stromal		7(11.1)
Granulosa cell tumor	7(87.5)	
Not indicated	1(12.5)	
Germ cell		7(11.1)
Dysgerminoma	4(57.1)	
Yolk sac/Endometrial sinus tumor	2(28.6)	
Immature teratoma	1(14.3)	
Others	5(7.9)	

Key: *nf:* frequency of histological subtype; N_H: Cumulative frequency of that histological type; N_T: Total number of study participants

The results of a bivariate analysis found a significant association between histology and parity [X2(6)=28.8, p<0.001]. Epithelial histology was the main histology observed among women of parity 1-5 (78%) and 6+ (80%). Germ cell histology was observed in 71% of the nulliparous women.

Table 3 Relationship between parity and histologic variants

Histologic variant	Parity Nulliparity	1-5	6+	Total
	n(%)	n(%)	n(%)	n(%)
Epithelial	0(0)	25(78.13)	12(80)	37(68.52)
Stromal	1(14.29)	5(15.63)	1(6.67)	7(12.96)
Germ cell	5(71.43)	1(3.13)	1(6.67)	7(12.96)
Others	1(14.29)	1(3.13)	1(6.67)	3(5.56)
Total	7(100)	32(100)	15(100)	54(100)

Over half, (63%) presented in stage 3 and 4 though there was no significant association between histology and stage of disease [X2(6) =4.72, p=0.58].

Table 4 Relationships between stage and histologic variants

	Stage				
Histologic variant	1	2	3	4	Total
Epithelial	3(60)	4(66.67)	4(80)	13(92.86)	24(80)
Stromal Germ	1(20)	1(16.67)	1(20)	0(0)	3(10)
cell	1(20)	1(16.67)	0(0)	1(7.14)	3(10)
Total	5(100)	6(100)	5(100)	14(100)	30(100)

Mortality was highest among women aged 35-44 years (26%), with secondary education (25%), and single (15.4%). However this was not statistically significant(p>0.05)

The 95 women in the study cohort contributed a total of 138.2 person-years to the study (Table6). 11 patients (12%) died during the course of the study, corresponding to a disease-specific mortality rate of 79.6 (95% CI: 44.1-143.8) per 1,000 person years.

The mortality rates were highest among women who had Epithelial histology 109 (95% CI: 48.8-241.9) per 1,000 person years and those who had chemotherapy first then surgery as a treatment option, 373 (95% CI: 93.3-1491.8) per 1,000 person years.

Figure 1 presents Kaplan-Meier survival curve for histology, stage of disease, and treatment options. The survival probabilities for women with sex cord stromal histology were generally higher than the survival probabilities for epithelial, germ cell and other histopathological subtypes.

Table 6 Mortality rates by type of histology, treatment option, parity, education and marital status

Variables	Person-time	Deaths	rate	[95% Conf. Interval]		N
Histology						
Epithelial	55.2	6	109	48.8	241.9	51
Stromal	23.1	1	43.3	6.1	307.6	7
Germ cell	27.4	1	36.5	5.1	259.3	13
Others	12.3	1	81.3	11.5	577.5	5
Missing	20.16	2	NA	NA	NA	19
Treatment option						
Primary surgery	47.2	3	63.6	20.5	197.1	28
Chemo first then surgery	5.4	2	373	93.3	1491.8	8
Interval debulking	0.1	0	0	NA	NA	1
Adjuvant chemo-therapy	52.6	4	76	28.5	202.6	32
Emergency surgery	0.2	0	0	NA	NA	1
Missing	32.66	2	NA	NA	NA	15
Parity						
Null parity	12.2	1	82.2	11.6	583.3	8
5-Jan	59.5	4	67.2	25.2	179.1	40
6+	33.8	2	59.2	14.8	236.8	22
Missing	32.66	4	NA	NA	NA	15
Education						
Primary	4.2	0	0	NA	NA	8
Secondary	25.6	3	117	37.8	363.8	12
Tertiary	20.4	1	49.1	6.9	348.7	10
None	13.8	2	145	36.2	578.7	11
Missing	74.16	5	NA	NA	NA	54
HIV status						
Negative	116.4	8	68.8	34.4	137.5	73
Positive	5.2	1	191	26.9	1356.8	8
Missing	16.56	2	NA	NA	NA	14
Total	**138.16**	**11**	**79.6**	**44.09**	**143.76**	**95**

Table 5 Distribution of deaths by selected covariates

| Variable	Chi-square (df)	p-value	Death n/N	Percent (%)
Age <35 35-44 45-54 55+	6.83 (3)	0.078	 2/20 5/19 3/21 1/35	 10.0 26.3 14.3 2.9
Total			**11/95**	**11.6**
Education Primary Secondary College/Tertiary None Not indicated	3.85 (4)	0.426	 0/8 3/12 1/10 2/11 5/53	 0 25 10 18.2 9.4
Total			**11/94**	**11.7**
Marital status Single Married/Living Separated/Widowed	0.74 (2)	0.69	 4/26 5/54 2/14	 15.4 9.3 14.3
Total			**11/94**	**11.7**
Employment status Employed Not employed	0.28 (1)	0.597	 2/14 7/73	 14.3 9.6
Total			**9/87**	**10.3**
Parity Null 1-5 6+	0.08 (2)	0.963	 1/8 4/40 2/22	 12.5 10 9.1
Total			**7/70**	**10**
Histology Epithelial Stromal Germ Others	0.57 (3)	0.902	 6/51 1/7 1/13 1/5	 11.8 14.3 7.7 20
Total			**9/76**	**11.8**
Stage 1 2 3 4 Not indicated	6.02 (4)	0.198	 1/5 0/6 2/6 1/14 3/46	 20 0 33.3 7.1 6.5
Total			**7/77**	**9.1**
Treatment option Primary surgery Chemo first Interval debulking Adjuvant chemotherapy Emergency surgery Not indicated	2.15 (5)	0.828	 3/28 2/8 0/1 4/32 0/1 1/16	 10.7 25 0 12.5 0 6.3
Total			**10/86**	**11.6**
Treatment plan Surgery Chemo Chemo/Surgery Follow-Up Palliative Hospice care Other	11.05 (6)	0.807	 3/34 4/33 1/6 0/7 2/3 0/1 0/4	 8.8 12.1 16.7 0 66.7 0 0
Total			**10/88**	**11.4**
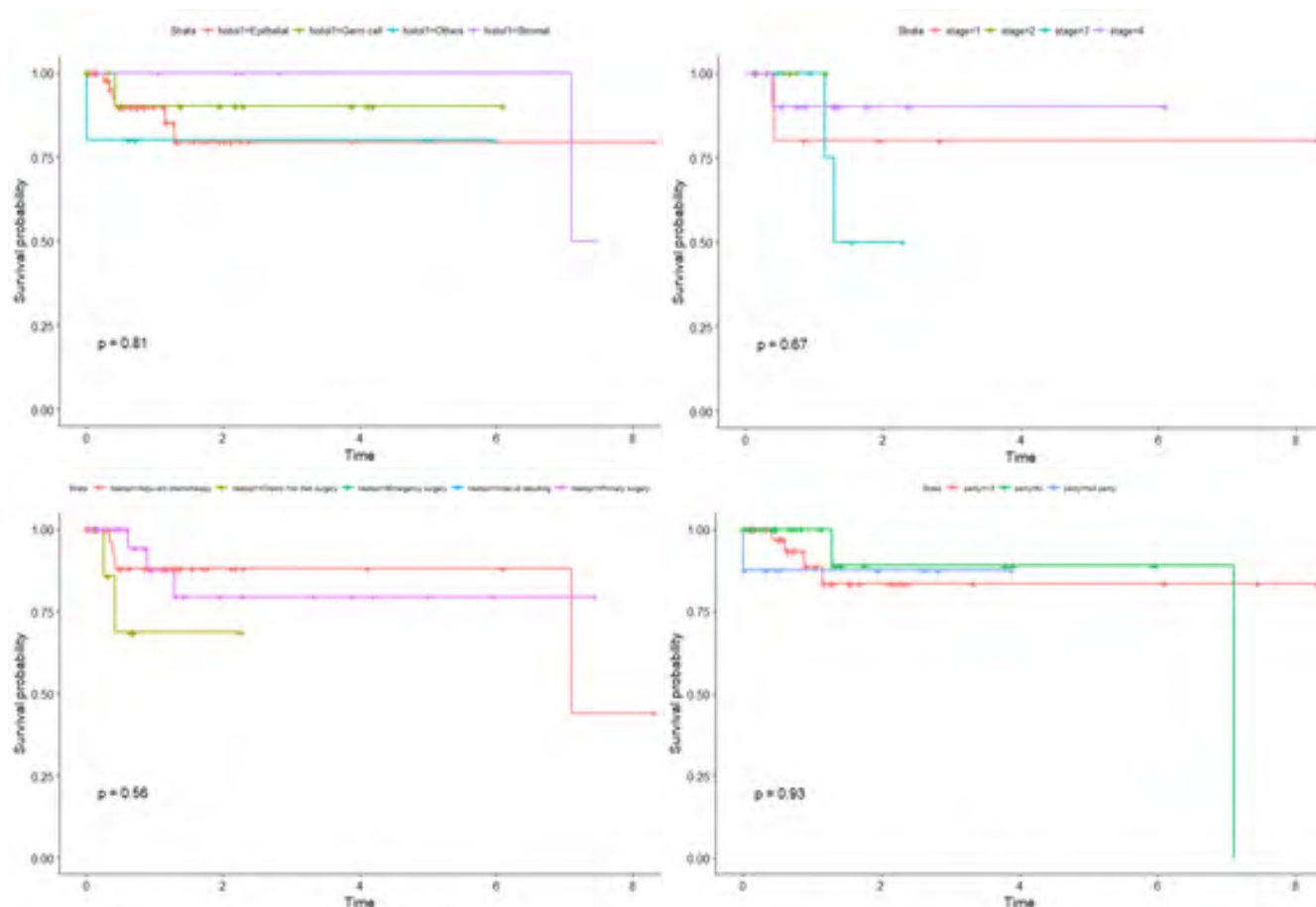
Figure 1 Kaplan-Meier survival curve for histology (top-left), stage of disease (top-right), treatment option (bottom-left), and parity (bottom-right)

Survival probabilities were generally lowest among women who had undergone neoadjuvant chemotherapy followed by surgery and women of parity 1-5.

DISCUSSION

Ovarian cancer is a common gynecological malignancy globally and the second most common gynecological malignancy after cervical cancer at MTRH (Rosen et al., 2017). Overall, Ovarian Cancer patients seen at MTRH (82.8%) were mainly referrals from Counties neighboring Uasin Gishu where MTRH is domiciled. This can be attributed to lack of expertise and equipment to manage ovarian cancer in the surrounding counties. In Kenya, level IV and V hospitals have limited capacity to provide cancer care (Cheserem et al., 2013, Rosen et al., 2017). The absence of staff (nurses and doctors) with specific oncology training and lack of equipment required for management of gynecological malignancies leave hospitals without human resources with appropriate skills to manage cancer patients(Cheserem et al., 2013, Rosen et al., 2017).

Ovarian cancer at MTRH is diagnosed at advanced stages whereby 63% were in stages III and IV of disease. This is similar to the study at KNH (Cheserem et al., 2013) and this is attributed to the disease being largely asymptomatic in early stages. Ovarian cancer is predominantly a disease of older, postmenopausal women with the majority of cases being diagnosed in women over 50 years (Alsop et al., 2012). In our study, the median age at diagnosis was 47 years with 55-80 years being the modal age group. This is similar to studies in developing world, the median age at Alexandria University hospitals in Egypt was 48 years and Pakistan where the median age at its National Cancer Institute was 49.5 years (Ramadan et al., 2015). The apparent shift to an earlier age of occurrence during the premenopausal period is a worrisome development.

Nulliparity as a risk factor for ovarian cancer has been associated with repeated cycles of ovulation, resulting in increased trauma and scar tissue formation on the surface epithelium of the ovary thereby increasing risk of malignant transformation (Alsop et al., 2012, Chan et al., 2006, O'Malley et al., 2003).

The findings of this study however demonstrated a significant association between epithelial type and increasing parity. Epithelial histology was still the main histology observed among multiparous women. Many epidemiological studies have reported a reduced risk of ovarian cancer amongst women who have had children, finding decreasing risk with increasing number of births. However our findings reflect an association between histopathological type and increasing parity. This trend has been described in many other cancer types including breast cancer and may be related to differences in population structure and risk-factors (Ahmed et al., 2013). Further genetic and epidemiologic studies are needed to explain these results as underlying genetic mutations vary between communities.

Consistent with findings from other studies in developing countries, the most common histological variant was epithelial ovarian cancer which accounted for 69.8% of cases (Fatigerun et al., 2015). Upon stratification, Serous Epithelial carcinoma was the most predominant subtype of epithelial ovarian cancer accounting for 50%. Mucinous, endometrioid, Unspecified, and others contributed 11.4%, 6.8%, 13.6% and 18.2% respectively. These findings are in agreement with a previous ten year study on ovarian cancer at The Kenyatta National Hospital, Nairobi which show that the population could be more or less similar (Cheserem et al., 2013). On the other hand, germ cell tumors were observed in 71% of the nulliparous women. As described by (Chan et al.,2006) the reported age of germ cell tumors ranges from 16 months to 46 years, but most patients are under 30 years of age and most likely nulliparous. On further disaggregation of germ cell tumors, Dysgerminomas, Yolk sac/Endodermal sinus tumors and Immature teratomas were observed in 57.1%, 28.6% and 14.3% respectively. Thus, together with findings in studies from the United States of America and India, this study has confirmed dysgerminoma as the commonest malignant germ cell tumour and Yolk sac tumor being is the second most common (Fatigerun et al.,2015, Gharoro et al.,2006,Chan et al.,2006).

In our setting, the only documented sex cord stromal tumor was granulosa cell tumor. This confirms the rarity of other sex cord/stromal subtypes and is in agreement with related work in Benin City, Nigeria (Gharoro et al.,2006). Notably in this study, the survival probabilities for women with granulosa cell tumors were generally higher than the survival probabilities for epithelial, germ cell and other histopathological types. Generally, ovarian granulosa cell tumors have a good prognosis in comparison with epithelial tumors. This is attributed to their indolent nature, most are found in early stage and exhibit late recurrences (Divya et al., 2003)

Chan et al reported that mortality of elderly patients with epithelial ovarian carcinoma is higher than that of their younger counterparts (Chan et al.,2006). However in our study, at MTRH, mortality among patients with ovarian cancer was highest among middle aged women. This variation is likely attributed to differences in the distribution of histological type or grade, International Federation of Gynecology and Obstetrics (FIGO) staging, and under treatment, but this observation remains controversial. In addition, it has been indicated before that younger age is not an independent prognostic factor for improved survival (Chan et al.,2006, O'Malley et al.,2003) suggesting that the survival advantage of the younger patients may be attributed to the increased frequency of early-stage, lower grade disease, and tumors of low malignant potential .

Serous ovarian cancer accounts for 70-80% of ovarian cancer deaths, and overall survival has not changed significantly for several decades (Brun et al., 2000). In this study, mortality rates were highest among women who had epithelial ovarian cancer. Neoadjuvant chemotherapy followed by interval debulking surgery has recently emerged as an alternative strategy to upfront surgery. Two large randomized trials found non-inferior survival for neoadjuvant chemotherapy compared with upfront cytoreductive surgery (Kehoe et al., 2015). The findings from our study show that those who underwent neoadjuvant chemotherapy followed by surgery had a higher mortality rate as compared to those who had upfront surgery. Additionally, the survival probabilities over the first two years were generally lowest among women who had undergone neoadjuvant chemotherapy. This can be attributed to the use of neoadjuvant chemotherapy in patients who are older, have a high perioperative risk, poor

performance status, have comorbid conditions, or a high disease burden in which an optimal resection is unlikely and this may contribute to the described mortality and survival in this group.

CONCLUSION: Ovarian cancer has advanced stage lower median age at presentation for patients seen at MTRH, most patients being referrals from other counties. Epithelial ovarian cancer (EOC) is the commonest histological type and serous subtype is the most lethal with lowest survival probability. Mortality was highest among those with EOC and those who underwent neoadjuvant chemotherapy. Granulosa cell tumor is the only sex cord stromal type reported in our setting and it exhibited a higher survival probability. Germ cell tumors were mainly found in nulliparous women.

LIMITATIONS: The main limitation of this study was inadequate documentation of vital information. Data were scanty on management outcome and records of deaths from ovarian cancer. This calls for increased vigilance in data entry and record keeping.

DECLARATION

The research idea was conceived by Benjamin O. Elly, data collection interface was designed by Thomas Achia and also did the analysis. Data collection was done by Hellen Namaemba and Joyce Musimbi, the manuscript was prepared by Benjamin O. Elly and reviewed by Peter Itsura, Elkanah Omenge, Tonui P.Kipkirui, and Oyiengo V.N .

All authors approved the manuscript.

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