TIITLE: REVIEW OF CLINICO-PATHOLOGICAL PRESENTATION, MANAGEMENT AND OUTCOMES OF PATIENTS WITH SEX CORD-STROMAL TUMOURS OF THE OVARY MANAGED AT KNH FROM 2010 TO 2020.

A DESCRIPTIVE RETROSPECTIVE CROSS SECTIONAL STUDY.

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DECLARATION

This research is my original work and has not been presented for academic award in any other University. References made to others work has been indicated.

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DEDICATION

I dedicate this work to all our gynaecological oncology patients that we are privileged to serve and to our teacher and mentor Dr. Amin Medhat who sadly was suddenly called to glory during our training.

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LIST OF ABBREVIATIONS

AFP	Alpha-fetoprotein
AGCT	Adult granulosa cell tumour
BEP	Bleomycin, Etoposide and Cisplatin
BRCA	Breast cancer gene
BSO	Bilateral salpingo-oophorectomy
CA-125	Cancer antigen 125
CEA	Carcinoembryonic antigen
CT	Chemotherapy
FIGO	International Federation of Gynaecology and Obstetrics
FOXL2	Forkhead box protein L2
FSS	Fertility sparing surgery
GCT	Granulosa cell tumour
hCG	Human Chorionic Gonadotropin
ICD 10	International coding for disease 10
IHC	Immunohystochemistry
JGCT	Juvenile Granulosa cell tumour
KNH	Kenyatta National Teaching and Referral Hospital
LDH	Lactate dehydrogenase
LND	Lymph node dissection
MIS	Mullerian inhibitory substance
RH	Reproductive health
RT	Radiotherapy
SCSTs	Sex cord stromal tumours
SEER	Surveillance, Epidemiology and End Results
SLCT	Sertoli-Lydeig Cell tumours
STK11	Serine-Threonine kinase 11
TAH	Total abdominal hysterectomy
TCT	Theca cell tumour
USO	Unilateral salpingoophorectomy
UON	University of Nairobi
WHO	World Health Organization

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ABSTRACT

Background: Sex cord-stromal tumours (SCST) represent a heterogenous group of tumour histological subtypes that develop from primitive sex cords, stromal cells or mesenchyme. They are indolent however most patients present in early stage because of symptoms caused by hormones produced by these tumours. Surgery is the mainstay of treatment. These tumours predominantly affect reproductive age women therefore fertility sparing surgery is a good option. There is paucity of data regarding SCSTs in our setup. The objective was to review the clinico-pathological presentation, management and outcome of these patients.

Methods and Materials: This was a descriptive cross sectional study where 55 study participants with SCSTs managed at Kenyatta National Hospital (KNH) between January 2010 and December 2020 were recruited. Data on clinico-pathological presentation, management and management outcome was reviewed from their medical records, captured on questionnaires, entered into SPSS software and analysed.

Results: Of the 1296 patients with ovarian tumours identified 55 had confirmed SCSTs representing 4.2%. Patients presented at a wide age range from 7-81 years but majority were young, most in their reproductive years and most were married. The median age was 46 years (IQR 33-59 years). Granulosa cell tumours (GCT) accounted for 80% (44/55), of which adult granulosa cell tumour (AGCT) was 39% (17/44) but 52% (23/44) of GCT were not sub-classified on reporting. Most patients presented at early stage. Abdominal pain (85%, 47/55) and abdominal distension (78%, 43/55) were the most common symptoms. Vaginal bleeding was found in 40% (22/55). A pelvic mass was palpable in 55% (30/55) of the patients. All underwent surgery out of which 32% (17/55) were fertility sparing (FSS). Information on tumor staging and grading was poorly documented, with only 9 reports indicating histologicalgrade. BEP was the most used adjuvant chemotherapy regime. Fourty (73%) of the documented study participants were alive at 2 years and 15 (55.6%) at 5 years. Some records could not be traced and others lacked critical details.

Conclusion: Sex cord stromal tumours are rare at KNH, have a range of age at diagnosis and clinic-pathological presentation. Treatment outcomes were good but accurate diagnosis and management requires good knowledge and a high index of suspicion..

Recommendations: Patients who desire fertility retention may be offered fertility sparing treatment. Improvement need to be made in medical records and patient follow-up.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Ovarian tumours are classified based on cell of origin into epithelial ovarian tumours, germ cell tumours and sex cord stromal tumours (SCSTs). Epithelial tumours make up 80% of ovarian tumours and the bulk of ovarian cancers (1, 2). SCSTs are a heterogeneous group of tumours that arise from primitive sex cords, the ovarian stroma or mesenchyme within the developing gonad. The sex cords and stroma support the germ cells and are covered by surface epithelium. Stromal cells include fibroblasts, Leydig cells, and theca cells, while sex cords cells comprise granulosa cells, and Sertoli cells. The cells may be present in a pure form or in different combinations and show diverse degrees of differentiation (3, 4, 5, 6).

Globally SCSTs make up 5-8% of all ovarian neoplasms (7). A study in Pakistan reported SCSTs make up 4% of ovarian neoplasms (3, 8). Every year, 15-20,000 new cases are reported in the USA (9), while in Ghana a study reported a higher figure of 15.1% of ovarian neoplasms (10). In a study on characteristics and management of ovarian cancers at KNH from 1998 to 2008, Cheserem et al, in 2013 reported SCSTs made up 1% of all cases of ovarian cancer (11).

To the best of our knowledge, there have been no studies in Kenya that specifically focus on SCSTs. This study therefore aims at reviewing the clinic-pathological features, management and management outcomes of these patients with SCSTs.

1.2 CLASSIFICATION OF SEX-CORD STROMAL TUMORS

The World Health Organization (WHO) in 2014 reclassified SCSTs into three clinical-pathologic sub-types namely pure stromal tumours, pure sex cord tumours, and mixed sex cord-stromal tumours (Appendix 1). Pure stromal tumours include fibromas, theca cell tumours, and Leydig cell tumour. Pure sex cord tumours include adult granulosa cell tumours, juvenile granulosa cell tumours and Sertoli cell tumours while mixed sex cord-stromal tumours include Sertoli-Leydig cell tumours and Gynandroblastomas. Rare SCSTs include Sclerosing SCSTs and SCSTs with annular tubules (6, 12, 13).

Fibromas are typically benign and hormonally inactive tumours that make up about 4% of all ovarian neoplasms. They are associated with Meig's syndrome which mimics malignancy but which typically is curable via surgical excision of the fibroma (6, 9, 14). Theca cell tumours on the other hand are benign neoplasms that exclusively contain theca cells. They account for 0.5-1% of ovarian tumours. They are similar to fibromas, but produce oestrogen (6, 9, 14).

Granulosa cell tumours are the most common SCST subtype making up 80% of SCST and comprising less than 5% of all malignant ovarian tumours. In studies in Pakistan and Ghana they made up 43% of cases (3, 8, 10) and made up 49.5% in Egypt (15).

On histology the pathognomonic feature of GCT is Call-Exner bodies which are small eosinophilic fluid-filled spaces between granulosa cells in rosette-like formations. The eosinophilic material consists of excess basal lamina in attempt of the neoplastic cells to form basement membrane (6, 9, 13).

They are low-grade indolent malignant tumours and are the most common estrogen-producing tumours. Majority are detected early and recurrences after treatment occur late.

GCTs are of two subtypes, Adult GCT and Juvenile GCT. Majority are adult type accounting for 95% of these tumours. They were reported to make up 95% in Germany (16), 90% in USA (17), 92% in Pakistan (3, 8) and 85% in Tehran (10). Adult GCTs are the most common malignant SCSTs and may be well-differentiated or less well differentiated on histology. Juvenile GCT occurs predominantly in children and young women less than 30 years, and is uncommon in adults (6, 9, 14, 17).

Pure Sertoli cell tumours contain only Sertoli cells and some patients present with elevated blood pressure due to production of renin by Sertoli cells. Pure Leydig cell tumours are rare, usually benign and occur in older women about 50 years. They are predominantly androgen-secreting tumours (6, 9,14).

Sertoli-Leydig cell tumours contain both Sertoli and Leydig cells. They are rare making up 0.5-1% of all ovarian neoplasms. Sertoli-Leydig cell tumours made up 10.0% in the USA (3, 8,17). Less than 5% are malignant while 30-50% produce androgens and are the most common virilizing ovarian tumour, occurring in more than 33% of cases (6, 9, 14).

Gynandroblastomas are rare types of SCSTs with both female and male cellular pattern displaying both granulosa and Sertoli cell elements observed in young women. It is thought that it originates from a single progenitor cell that differentiates into both female and male elements. For diagnosis the minor tumor component (either Sertoli-Leydig cells in a GCT, or granulosa cells in an SLT) should make up at least 10% of the tumor. They are malignant and are hormonally active and so patients present with either estrogenic or androgenic symptoms (6, 9, 14).

1.3 ETIOLOGY AND PATHOGENESIS

The molecular pathogenesis and risk factors for SCSTs are unclear. Previous studies have indicated possible gene mutations involving FOXL2, DICER1 and STK11 genes (17, 18, 19). *FOXL2* is a transcription factor that is restrictedly expressed in granulosa cells during development and adulthood. *FOXL2* mutation C134W (402 C > G) found in GCTs especially adult type-GCT may alter antiproliferative pathways and limit apoptosis, which contributes to the pathogenesis of adult granulosa cell tumours. SLT and gynandroblostoma are associated with somatic or germline mutations of *DICER1*, which encodes an RNase III endonuclease that is critical for microRNA processing. Mutations result in systemic loss of 5p-microRNAs that precludes regulation of growth promoting gene programs. Mutations of *DICER1* occur in about 60% of SLTs. Mutations in STK11 include deletion and/or duplication and are commoner in sex-cord tumours with annular tubules. All these biological markers have the potential to be of diagnostic and prognostic marker and have therapeutic value.

Data from SEER suggest that the incidence of sex cord-stromal tumors is significantly lower among white women compared with black women (0.18 v 0.35 per 100,000 person years; relative risk, 0.53; 95% CI, 0.42 to 0.67). (17). The data showed that unlike what has been observed with epithelial ovarian cancers, BRCA1 or BRCA2 gene mutations has no significant association with SCST (17, 20).

CHAPTER 2 : LITERATURE REVIEW

2.1 CLINICO-PATHLOGICAL PRESENTATION

Studies show that SCSTs affect patients through a wide age range including children, adolescents, young adults and older women. The range was reported as 9-93 years in the USA (17), 1-92 years in Pakistan (3, 8), 16-76 years in Ghana (10) and 13-84 years in Egypt (15). A Cochrane review reported GCT to occur at a range 20-74 years (21). In a study in India age of presentation varied from 4 to 70 years (22).

Majority tend to present in younger patients usually in the first two to three decades of life. Among women with SCSTs, 12% are younger than 30 years and 57% are between ages 30 to 59 years (17). In a study in the USA 50% of patients were less than 50 years (20). Median age of presentation have been reported as 45 years in Pakistan (3, 8), 41 years in Tehran (23), 47 years in Egypt (15), 40 years in Ghana (10) and 51 years in the USA (20). Adult granulosa cell tumours however typically present later (6, 14, 17). Studies have reported a peak age 50 to 55 years in the USA (17), a median of 48 years in Pakistan (3, 8) and 46.5 years in Ghana (10). In contrast epithelial ovarian tumours affect older women usually 50-70 years (17).

Most malignant SCSTs present as low-grade disease that is not clinically aggressive and is confined to the ovary in 57% of women. Tumours are usually unilateral (17). Studies in India reported this in 96% of cases (4). Patients are often diagnosed at early stage. In Egypt 95% had early disease (64.5% stage 1, 31.25% stage 2) (15) while in the USA 80.9% had early disease (70.5% stage 1, 10.4% stage II, 11% were in stage III and 8% were in stage IV) (20) and in Tehran 87.1% were in stage I (23)

Studies show that SCSTs have diverse clinical features. SCSTs may present with symptoms of a pelvic or abdominal mass like pain, discomfort, abdominal swelling and gastrointestinal symptoms (6, 14, 17). In a study in Pakistan a mass and pain was found in 67% of cases and distension in 54% of cases (3, 8). In India a mass and pain made up 51.3% of the presentation (4) while in Egypt abdominal pain was found in 54.5% and a mass in 53.2% of cases (15). Large tumours may undergo torsion or rupture, resulting in an acute presentation with pain and haemoperitoneum (6, 14, 17).

Some SCSTs produce steroid hormones mainly androgens, estrogens or corticosteroids, and as a consequence may present with a wide spectrum of clinical features and signs of excess hormone production. Excess estrogen production may lead to sexual precocity in children, abnormal uterine bleeding, endometrial hyperplasia in 22%, and even endometrial carcinoma in 2.5% while those with excess androgens may present with features of virilization. These clinical features distinguish SCSTs from ovarian epithelial neoplasms. In a study in India, 31% of patients had abnormal menses. In Pakistan menstrual abnormalities were common but hormonal changes were rare, while in Egypt menstrual abnormalities were associated with GCT. In a study in India a young girl only 4½ years had precocious puberty (3, 5, 6, 8, 14, 15, 22, 17).

2.2 DIAGNOSIS

SCSTs may be suspected preoperatively by clinical features like presence of an adnexal mass, signs of estrogen or androgen excess and characteristic features on imaging. These tumours elaborate serum tumour markers that may assist in preoperative diagnosis. Definitive diagnosis, tumour subtype and whether benign or malignant and grade however is confirmed

only after histology. Frozen sections where service available may be taken in theatre to guide surgical management (6, 14, 17).

Histopathologic diagnosis of SCSTs may be challenging. Immunohistochemistry is useful in improving diagnostic accuracy especially when HPE is inconclusive of the type and Inhibin as an IHC marker is positive in most SCSTs (17, 18). In a study in Pakistan all subtypes were Positive for Inhibin (3, 8). In India they reported IHC sensitivity of 90% and specificity of 100% for Inhibin while for FOXL2 Sensitivity and Specificity were both 100% (19).

2.3 MANAGEMENT

2.3.1 Laboratory evaluation

Serum tumour markers including cancer antigen 125 (CA-125), Inhibin, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), human chorionic gonadotropin (hCG) and lactate dehydrogenase (LDH) should be analysed. Serum calcium levels may help to distinguish SCSTs from small cell carcinoma of the ovary (6, 17, 18). In a study in Egypt 55.8% had elevated CA-125(15). In a study by Dimitrios in early stage disease elevated preoperative CA-125 was associated with worse outcomes (24). Estradiol, Testosterone and Mullerian inhibitory substance (MIS) may also be assayed (6, 17).

2.3.2 Imaging

Ovarian SCSTs may show characteristic features on imaging. Recognition of the spectrum of clinic-pathological features and imaging appearance may assist when coming up with a differential diagnosis in these tumours (6, 25). In a study in Egypt imaging was able to pick up all masses (15).

2.3.3 Surgery

Surgery in SCSTs is performed for staging, diagnosis and management (5, 12, 16, 26, 30). Staging of SCSTs is done utilising the FIGO staging as used for epithelial ovarian tumours (12, 31). (Appendix 2)

The primary treatment is surgical and outcomes are favourable in contrast to epithelial ovarian tumours (5, 12, 16, 26, 30). Surgery performed may be fertility sparing surgery (FSS) or non fertility sparing (non-FSS). In studies on FSS 34% of patients underwent this in the USA (20), 40% in Tehran (23), 23% in Italy (26) and 30% in Egypt (15). Suitable patients for fertility sparing surgery were in their reproductive age, had unilateral tumour, intact capsule and had no metastasis (15, 20).

Counseling on risks of conservative surgery must be done. Though SCST usually involve one ovary, in 2-8% both ovaries are involved. Endometrial biopsy should be performed to rule out endometrial cancer co-existing with the SCST. Consideration should be made for a completion TAH with USO after childbearing (5, 26, 27, 28).

Excision of all gross tumours should be performed where the procedure is considered safe. Patients who have completed child bearing may undergo TAH with BSO. Children, adolescents, and young women who desire to retain fertility, may undergo FSS. Fertility sparing surgery is appropriate if disease is local to one ovary as is usually the case in 90% of patients (5, 26, 27, 28).

FSS involves the complete removal of the affected tube and ovary and not just ovarian cystectomy. In some centres FSS is also attempted in stage II and III disease among

children where there is no significant involvement of the uterus and the opposite tube and ovary. Following all surgery, the surgical notes should clearly state whether there was any rupture of the ovarian capsule and where there is rupture if preoperative (FIGO stage Ic2) or intraoperative (FIGO stage Ic1) (5, 26, 27, 28).

Routine lymph node dissection (LND) can be omitted in SCST. There is a very low risk of metastasis to the lymph nodes with primary SCSTs. In a study by Dimitrios LND was performed in 49.5% of their cases but lymph node metastases were present in only 3.3%. 5 year survival was similar, 92.7% with LND and 94.7% without LND. Enlarged lymph nodes picked on imaging or encountered during surgery should however be dissected out (5, 26, 27, 28, 29).

2.3.4 Chemotherapy

Adjuvant chemotherapy (ACT) is indicated in Stage II–IV disease and Stage I disease with a big tumour size, high mitosis, high-grade histology, SLCT tumour subtype, tumour rupture and incomplete surgical staging (20, 30). Studies have reported use of ACT as 46.7% in Egyptian (15), 51.9% in the USA (20) and 35% in an Italian study (26).

In most studies standard chemotherapy (CT) involves platinum-based treatment with Bleomycin, Etoposide and Cisplatin (BEP). Carboplatin and Paclitaxel combination have in recent studies been found to be as active in SCSTs as BEP and yet shown less toxicity (5, 12, 21, 26, 30, 31, 32, 33).

In an American Study on early stage disease, 5 year overall survival (OS) among those who got ACT and those who did not was similar at 81.7% compared to 84.6% (ref). There was however a difference in OS with advanced stage disease between those who got CT and those who did not get ACT with a median OS of 34.96 months compared to 15.51 months (20, 31). A Chinese study however showed ACT did not protect against recurrence in AGCT (36).

2.3.5 Radiation therapy

The place of adjuvant radiation therapy (RT) remains controversial though granulosa cell tumours are radiosensitive (20). Radiotherapy has been used for local advanced? stage or localrecurrent disease. In a study in Tehran 9.7% of their patients received radiotherapy (23) while in a study by Zhagalo in Italy 35% needed chemotherapy and RT (26). 2.1% got RT in a USA study (20).

There have been reports of improved survival where RT is used in selected patients, however there are no good published prospective studies with recommendations as to radiation dose or regimen for use in ovarian SCST after diagnosis to support routine (5, 12, 16, 26, 30).

2.4 FOLLOW-UP

Patients are monitored clinically, radiologically and with tumour markers. In the first 2 years imaging and laboratory evaluations are done every 3 months or more frequently if clinically indicated. After the first 2 years patients are monitored every 6 months (5, 12, 16, 26, 30).

Recurrences or metastasis of SCSTs have been found to be rare. After initial management, adult GCT may relapse, often after more than 10 years going up to 30 years later while Juvenile GCT most frequently recur within the first few years. Recurrence after a diagnosis

of SLCT in most patients happens within the first few years in most of the patients. Relapse with stage IC can be as high as 30-40% (5, 12, 16, 26, 30). Recurrence was reported to be 5% in Pakistan (3, 8) and 20% in Egypt (15).

2.5 MANAGEMENT OUTCOME

The outcome of SCSTs is favourable since they mostly present early while still involving one ovary, and are chemosensitive. Factors that influence survival include patient age at diagnosis, FIGO Stage, rupture of capsule, histological subtype, tumour differentiation, residual tumour after surgery and recurrence (5, 16, 26, 35).

In a German population based study of survival data of invasive SCSTs from 1978 to 2005, they reported a 5 year OS of 55.8% and a 10 year OS of 42.8% for women diagnosed before 1988 and 89.1% and 78.3% respectively for women diagnosed after 1988. They attributed improvements in survival to more favorable stages at diagnosis and to advances in treatment such as improved surgery. There was no evidence for any benefit of adjuvant chemotherapy (16).

Age less than or equal to 50 years and disease at an early stage are significant factors that improve overall survival. Patients less than 50 years had survival rates 93-97% while those aged over 50 years had survival rates 84-92% in studies in USA and Germany (16, 20).

In study on early stage disease in the USA survival for those aged less than 50 years was 97% while that for those aged over 50 yearswas 92%. Patients younger than 50 years were noted to have a 10 year survival that was better than those more than 50 years (81% compared to 64%) (20).

FIGO stage influences survival. 5 year survival rates for early stage tumour have been reported as 90-95% for early stage while in late stage disease it is 25-59% (21, 24). Comparing patients with stage I to II with those with stage III to IV, those with stage I to II had a 36% survival advantage (20).

The type of Surgery has no effect on survival in early stage disease. Among patients undergoing fertility sparing surgery in the USA, Mallory reported survival for stage I-II of 94.8% while survival for stage I-II after non-fertility sparing surgery was 94.9%. Fertility sparing surgery is therefore a safe alternative in these young patients (20, 23).

Studies have shown that performance of pelvic lymph LND and use of adjuvant chemotherapy have no difference on overall survival. In a USA study 5 year survival in both groups was 97% and 98% which were similar (20).

Tumour Grade affects survival. In a USA study 5 year survival with Grade 1-2 tumour was 96% while with Grade 3 was 64%. In the same study the 10 year survival with Grade 1-2 tumour was 86% while with Grade 3 tumour it was 59% (20).

Tumour subtype has influence on survival. With GCT, studies report over 80% present at FIGO stage I and 5 year survival rate exceed 90%. Mortality with juvenile GCT is only 1.5% with stage IA (20). TCTs and Fibromas are often benign and therefore their 5year survival is nearly 100%.

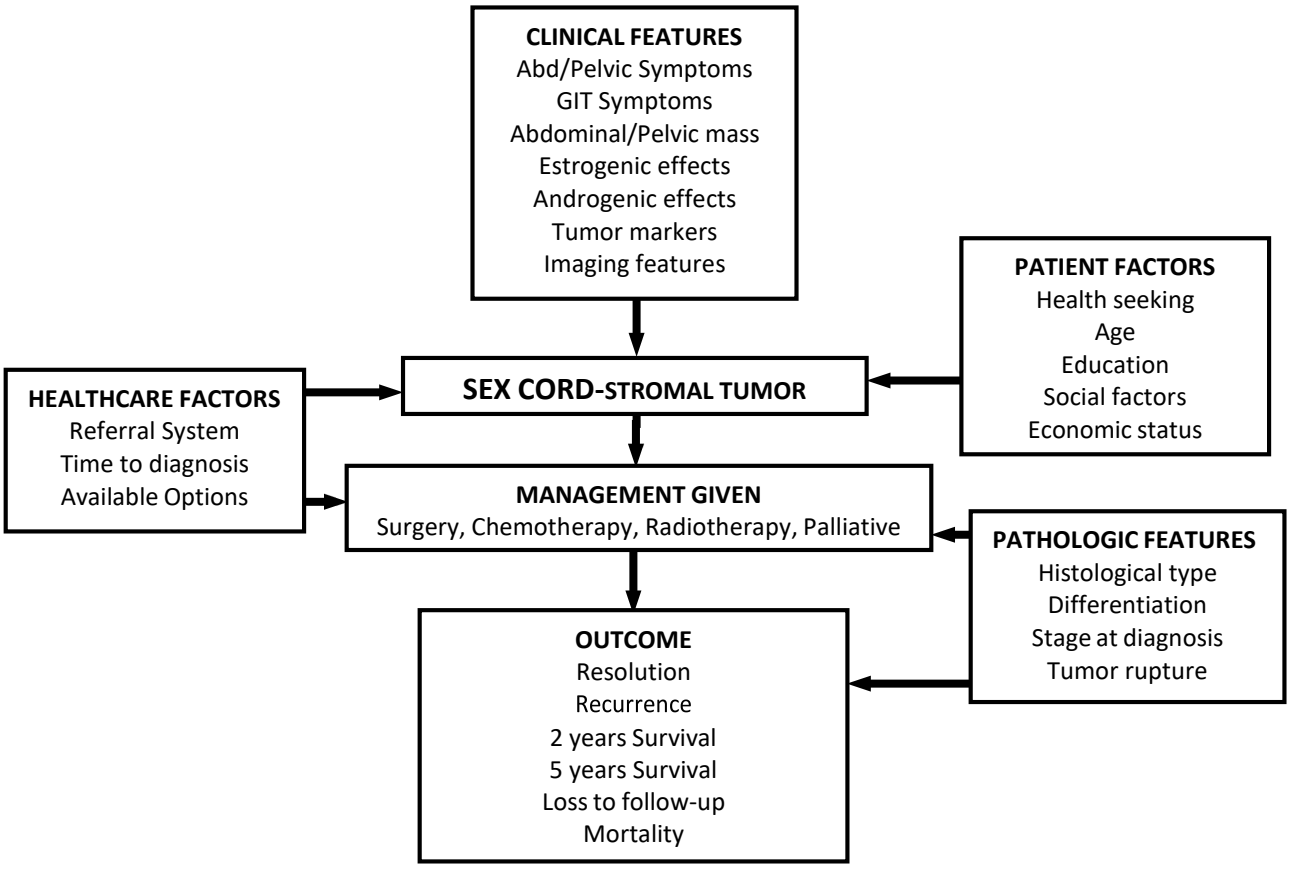
With Sertoli-Leydig cell tumours (SLCT), 5 year survival is 92.3% for FIGO stage I and 33.3% if more than stage 1. Survival is 100% if well differentiated and 77.8% if moderately and poorly differentiated. In a study at AKUH Pakistan on SLCT only 8.8% were well differentiated and 44.1% were intermediate (3, 8). Most patients presented at FIGO Stage 2 or higher.In a study in Egypt DFS was 50.5 months and OS was 49.5 months among patients with SLCT (15).

2.6 CONCEPTUAL FRAMEWORK

2.6.1 Conceptual Framework Narrative

SCSTs though rare are of major concern among relatively young women. The diagnosis is based on clinical features from history, clinical examination, lab investigations, tumour markers, imaging, surgical staging and ultimately histology. Patient factors like health seeking behaviour influence time to diagnosis and management. Healthcare factors like referral systems, time to diagnosis, available options determine manage offered and optimal management. Surgery is the mainstay of management but chemotherapy and radiotherapy are also used. Management is further influenced by factors like patient age, stage at presentation and histological type. Management outcome and long term survival is dependent on factors like patient age, stage at diagnosis and histological type. Most patients undergo resolution, but some get recurrences. Mortalities do occur during follow-up

2.6.2 Figure 1 - Conceptual Framework Figurative



2.7 STUDY JUSTIFICATION

SCST are considered malignant neoplasms that are amenable to surgery, are chemosensitive and have a favorable long-term outcome. These tumours affect more young women and this has implications on their desires for child bearing and ovarian hormone production.The rarity of these tumours, indolent nature, diversity of histological types, wide range of age distribution and variable biologic and clinical behavior however limits our knowledge of their natural history, optimal management options and outcome. Current management principles are derived from information from clinical management of other ovarian tumours yet good knowledge of SCSTs is critical for diagnosis and management to avoid inappropriate treatments of these relatively young women.

There is paucity of data in our setting hence limiting evidence based management. No studies have specifically addressed these tumours. Cheserem (1998 - 2008) looked at ovarian cancers at KNH in general.

There is lack of data on these tumours in our setting. This will be the first study focusing on ovarian SCSTs at KNH. Findings from this study will provide baseline data that is useful in informing our management outcomes and developing management guidelines for these specific ovarian tumours.

2.8 RESEARCH QUESTION

What are the clinico-pathological characteristics, management and management outcomes of patients managed for ovarian sex cord-stromal tumours at KNH from 2010 to 2020?

2.9 STUDY OBJECTIVES

Broad objective:

To review the clinico-pathological characteristics, management and outcomes of patients with primary ovarian sex cord-stromal tumours managed at KNH from 2010 to 2020.

Specific objectives:

Among patients managed for primary ovarian sex cord-stromal tumours at KNH from 2010 to 2020.

1) To describe the sociodemographic, and clinical-pathological characteristics
2) To describe the treatment given
3) To evaluate the management outcome at two and five year

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN

This was a descriptive cross sectional study. Patients with primary ovarian sex cord-stromal tumours were identified from medical records and their clinical records reviewed to determine their clinico-pathological characteristics, management and management outcomes.

All medical records of patients with ovarian tumours managed at KNH from Jan 2010 to Dec 2020 were retrieved from the registry and used to retrospectively abstract all data on ovarian tumours from which those of primary ovarian sex cord-stromal tumours were identified and included in the study.

The patient age at diagnosis, social-demographic data, date of initial diagnosis, the presenting symptoms, history, physical examination findings, lab reports, reports of tumour markers, imaging reports, stage at presentation, operative findings, presence of ascites, surgical management done, the histopathology reports with subtypes, chemotherapy regimens, recurrence details, treatment after recurrence, and mortality were collected and studied.

3.2 STUDY SITE AND SETTING

The study was carried out at Kenyatta National Hospital (KNH). KNH is the largest National referral hospital in Kenya and is located in Nairobi. It also serves as a teaching hospital of the University of Nairobi. The hospital has a bed capacity of about 1,800 patients, though often this bed capacity is surpassed. About 600,000 outpatients and 70,000 in patients are attended to each year. The hospital receives about 14,000 referrals from within and outside of Kenya.

The reproductive health (RH) unit at KNH offers a wide range of specialized services in obstetrics and gynaecology. These services are offered from various service points. At the Accident and Emergency Department the RH unit has a dedicated consultation room where triaging of patients for treatment and discharge, clinic follow-up or ward admission is done. Non urgent gynaecologic oncology patients including cancer of the ovary are followed up at the gynaecology oncology outpatient clinic (Clinic 18) once a week on Fridays. At the clinic new patients are reviewed and management plans made, and follow ups of old patients is also done. Patients with acute conditions such as acute vaginal bleeding, anaemia, deep venous thrombosis, acute infections, intestinal obstruction and respiratory embarrassment are admitted (to ward 1D) while scheduled elective gynaecology patients are admitted (to ward 1B) for surgical intervention and chemotherapy. The wards admit and manage about 5000 reproductive cancer patients a year of which 2000 are cancers of the ovary. Radiotherapy services are provided at the radiation oncology department.

The medical staff compliment of the unit is comprised of two gynaecologic oncologists, eight gynaecologic oncology fellows, and obstetrics and gynaecology residents.

A multidisciplinary team approach is employed in care incorporating general surgeons, plastic surgeons, urologists, uro-gynaecologists, intervention radiologists, pathologists, nutritionists, psychosocial support, palliative care specialists and other auxiliary services

The records department at KNH has a centralized filling system. Each patient at registration is assigned a unique patient number that forms a reference for that particular patient within the hospital for all services, all admissions and all subsequent hospital visits. After service

provision all patient files are returned to the records department and coded as per ICD10 and ICP in medicine. Indexing is subsequently done electronically.

The statistics unit is mandated with the task of availing the data for planning and research. The department of research has been keeping reproductive cancer data since 2009 utilising the Research Electronic Data Capture (RED Cap) software. There are about 2000 individual case records of ovarian cancer patients. The database captures variable including demographic characteristics, clinical characteristics, histopathology, surgical management, Chemotherapy management, follow up and treatment outcomes.

3.3 STUDY POPULATION

Patients with primary ovarian sex cord-stromal tumours managed in KNH from January 2010 to December 2020 formed the study population.

3.3.1 Inclusion Criteria

1. All patients with primary ovarian sex-cord stromal tumours with confirmed histopathology results managed in KNH between 2010 to 2020

3.3.2 Exclusion Criteria

The following were excluded:

1. Missing files
2. Missing histopathology report

3.4 SAMPLE SIZE CALCULATION

The sample size was determined by using a statistical formula as used by Yamane T 1967 as given in the equation below.

$$\mathbf{n_o} = \frac{\mathbf{z^2} \times \mathbf{p(1-p)}}{\mathbf{\mathcal{E}^2}}$$

Where

n = required sample size

p = prevalence of primary ovarian SCSTs estimated at 6.50% (average of the range 5-8%).

C² = confidence level at 5% expressed as decimal

Z = confidence level at 95% (standard value of 1.96)

Substituting the values into the equation above

$$\mathbf{n} = \frac{1.96^2 \times 0.065\ (1 - 0.065)}{0.05^2}$$

We got 93.39

= 94 patients

Since in this case we had finite population (N is known), we further used the equation below to adjust the sample of the finite populations,

$$n = \frac{n_0 N}{n_0 + (N - 1)}$$

This gave us 46.229

= **47** minimum patient files were to be reviewed.

3.5 SAMPLING PROCEDURE

A two-stage sampling procedure was used. All files of patients with ovarian tumors managed in KNH from 2010 to 2020 were listed and a majority retrieved. Those with histologically diagnosed ovarian sex cord-stromal tumors were picked and their records were reviewed and analysed.

Even though the calculated minimum sample size was 47, all patients managed with primary ovarian SCSTs managed in KNH from January 2010 to December 2020 were eligible for the study and their patient records were be analysed.

3.6 DATA COLLECTION AND MANAGEMENT

3.6.1 Data Collection instrument (Appendix 3 – Data Abstraction form)

Data was extracted from patient files and collected by way of a pre-printed questionnaire. Each patient had a separate data collection questionnaire. The questionnaire captured data on social demographic characteristics, obstetrics and gynaecology characteristics and clinical aspects. Clinical data included presenting symptoms, physical findings on examination, laboratory test results and imaging findings. The questionnaire captured data on surgical staging and treatment given whether surgical treatment, chemotherapy, radiotherapy, chemo-radiation or palliative care. The type of surgery performed was also captured. Aspects of pathology captured included the histological type and tumour grade. Use of chemotherapy and type of chemotherapy was also captured. Outcome after treatment data captured data on disease resolution, disease persistence, recurrence and mortality at 2 and 5 years.

Survival data was collected by perusing the patient files and extracting data for the last hospital visit recorded to determine if still on follow or if the patient died. For patients lost to

follow-up, calls were made using the contacts captured in the patient file. After verbal consent questions were asked on the status of the patient whether alive and well, had recurrence or was deceased and if deceased whether it was related to illness from the tumor.

3.6.2 Data Management

The Principal Investigator and two research assistants were responsible for data collection. The two research assistants had a medical background and further were trained by the principal investigator on sex cord stromal tumours and on study procedures and study ethics for purposes of this study. The Principal Investigator was responsible for the day to day running and supervision of the study.

Data on all ovarian tumour patients managed at KNH during the study periods were obtained from the Redcap database, the Oncology clinical 18 registers, Ward 1B and 1D patient admission registers, The file numbers were recorded and the patient records acquired from the registry. Data from the patient records with SCSTs was captured in the prepared data abstraction form. Each eligible patient record had a separate data abstraction form completed. At the end of each data collection day, the Principal Investigator reviewed the abstraction forms for missing data.

Each patient was assigned a unique identifier as a study number to maintain confidentiality. Abstracted data from the prepared forms for patients with SCSTs was entered and captured by Redcap and stored in a password protected Excel data base. Data was de-identified for analysis and analysis done using STATA Version 13. Data Visualization was done by use of Tables, Pie Charts and Graphs.

3.7 DATA ANALYSIS METHOD

Data was de-identified for analysis and missing data was quantified. Ninety percent completeness rule was observed. Descriptive statistics was used to describe different clinic-pathologic characteristic like symptoms, histopathological type, stage and treatment categories. Proportions were reported for categorical data while mean, IQR and standard deviation were reported for continuous variables. Treatment outcomes were analysed. Survival analyses to determine 2 and 5 year survival could not be done using Kaplan Meier's method due to the small number sample size and low number of deaths. Comparative relationship between categorical and quantitative data could not be done due to low power of study.

3.8. DATA VARIABLES

Table 1: Exposure and Outcome variables with sources of data according to objective

Specific objectives	Variable	Type of variables	Sources of data
1.Clinico-pathological Presentation	Social demographic data - Age - Marital status - Level of Educational - Employment status.	Independent	Patient files
	Obs and Gyn data - Parity - Age at Menarche - Contraceptive use - Age at menopause	Independent	Patient files
	Presentation – Abdominal Symptoms – Per Vaginal bleeding – Estrogenic features – Androgenic features	Independent	Patient files
	Physical Exam – Pelvic mass – Abdominal mass – Ascites – Chest signs	Independent	Patient files
	Lab Investigations – CA 125	Independent	Patient files

	– Inhibin – AFP – CEA – Estradiol		
	Imaging – Chest X-ray – Ultrasound – CT scan – MRI – PET Scan	Independent	Patient files
	Tumour Surgical Staging – Stage 1 – Stage 2 – Stage 3 – Stage 4 – Not Staged		Patient files
	Fluid for Cytology – Washout done – Ascites fluid present – Positive – Negative – Not taken	Independent	Patient files
1.Clinico-pathological Presentation	Histological types – Granulosa Cell Tumour – Fibromas – Theca cell tumour – Sertoli cell tumour – Leydig cell tumour – Sertoli Leydig cell tumour – Gynandroblastoma – Others types	Independent	Patient files
	Tumour Grade – Grade 1 – Grade 2 – Grade 3 – Not graded	Independent	Patient files
2.Management	Treatment given – Surgery – Chemotherapy – Radiotherapy – Chemoradiation – Palliative Care	Independent	Patient files
	Type of Surgery – Unilateral Oophorectomy – Bilateral Oophorectomy – TAH + BSO – TAH + BSO+Omentectomy	Independent	Patient files

	– Exploratory lap + biopsy – Others		
	Chemo Regimens 1st line – BEP – CP – VAC – Other	Independent	Patient files
	Chemo Regimens 2nd line – CP – VAC – Other	Independent	Patient files
	Number of chemo cycles – < 4 – 4 – 6 – > 6	Independent	Patient files
3.Outcome	Status after treatment – Alive – Recurrence – PersistenceDied – Lost to follow-up	Independent	Patient files

3.9. RESEARCH ETHICS (Appendix 4 - KNH / UON-ERC approval)

This study was submitted to the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UON-ERC) for approval. The study only commenced after approval was given. Permission to carry out the study was also sought from KNH. This study however was retrospective and therefore paused minimum risk to the patients.

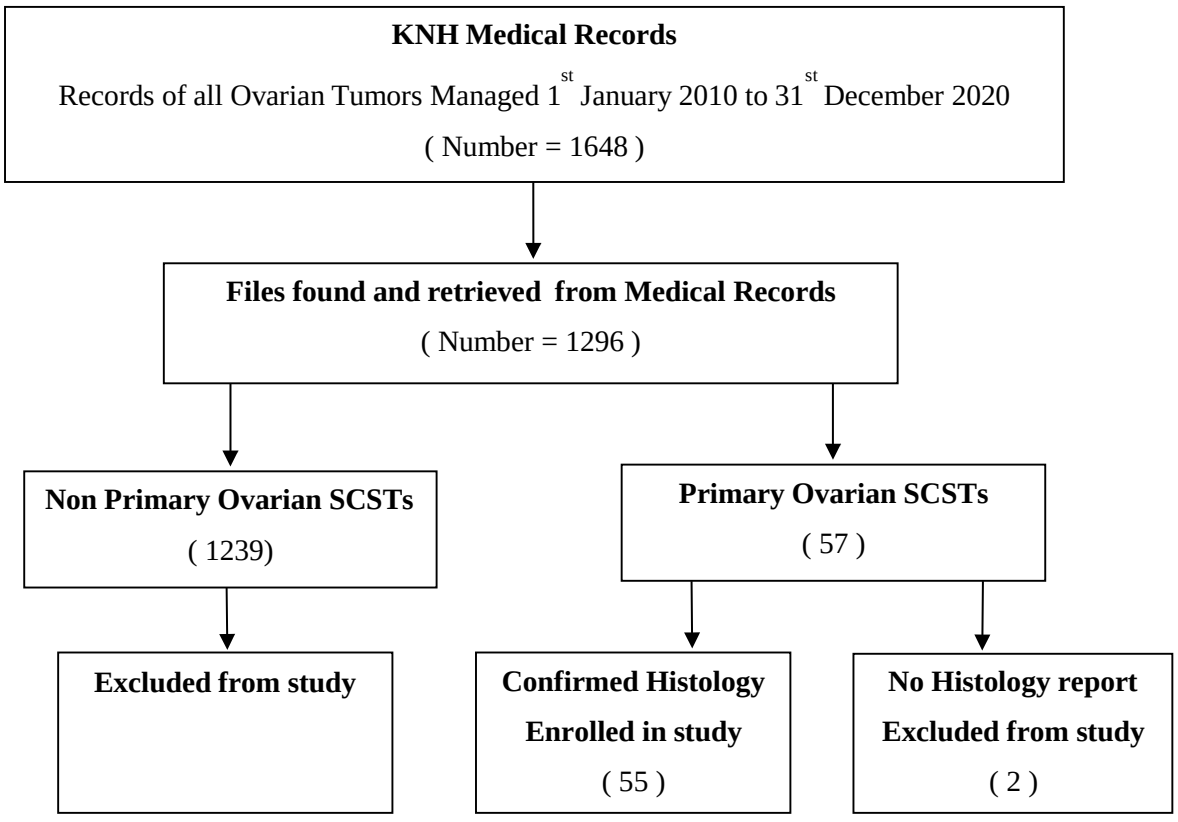
For patients lost to follow-up, telephone calls were made using the contacts captured in the patient file and after verbal consent. Information was then politely and sensitively sort on survivorship. A verbal phone consent form was developed. (Appendix 5)

The data and results were kept confidential at all times. No patient identifiers were collected or analysed and all research data was kept by the Principal Investigator in a lockable cupboard while all electronic data was Password protected.

RESULTS

A total of 1648 case records of all ovarian tumours managed covering the study period were identified. Out of these 1296 patient files were found and reviewed. Most had other histological types not SCSTs and were excluded from the study. Fifty seven were diagnosed with ovarian sex cord stromal tumours of which 55 patients had confirmed histology reports. Two had no histology report and were excluded. All the 55 records were analysed for all relevant information in the record.

Figure 2 - Study Flow Chart



Sex cord-stromal tumours represent 4.2% of all ovarian tumours at KNH in our study.

Table 2: File retrieval analysis by year for study on primary ovarian sex cord-stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

Year of diagnosis	All ovarian tumours	Sex cord-stromal tumours	
		Number	(% of ovarian)
2010	104	3	2.9
2011	111	3	2.7
2012	115	4	3.5
2013	119	4	3.4
2014	124	7	5.6
2015	121	6	5.0
2016	113	6	5.3
2017	120	5	4.2
2018	122	7	5.7
2019	124	5	4.0
2020	123	5	4.1
TOTALS	**1296**	**55**	**4.2**

Social-demographic characteristics

The median age was 46 years with a range of 7 to 81 years. A majority of patients (20/55) (36%) were in the age range 25 to 45 years. Sixty six percent (36/55) of the patients were married and 40% (22/55) had attained secondary education. Almost half of the patients (49%) (27/55)were not employed. Family history of cancer was poorly documented, with more than two thirds having no documentation (Table 3).

Obstetric and gynaecologic characteristics

Fourty percent (22/55) of patients had parity more than 4. Median age of menarche was 14 years (IQR 13 to 15 years) but this was documented in only half the cases. Not all had contraceptive use documented and for those documented, an equal proportioin of 36% (20/55) reported ever having used or not used contraceptives. Over 80% of those who used had used a hormonal method of contraceptive (Table 3).

Table 3: Social-demographic characteristics of patients with ovarian sex cord-stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

Characteristic	Value	n=55	(%)
Age at diagnosis (n=55)	5 -12 years	2	(4)
	13-24 years	5	(9)
	25-45 years	20	(36)
	45-60 years	15	(27)
	Over 60 years	13	(24)
Median, (IQR)	46years, (33-59years)		
Marital status	Married	36	(66)
	Separated/Divorced	2	(4)
	Single	12	(22)
	Widowed	4	(7)
	Missing	1	(2)
Highest level of Education	None	6	(11)
	Primary	17	(31)
	Secondary	22	(40)
	Tertiary	7	(13)
	Missing	3	(10)
Employment status	Formal employed	4	(7)
	Self employed	17	(31)
	Unemployed	27	(49)
	Missing	7	(13)
Family history of cancer	Yes	1	(2)
	No	15	(27)
	Not stated	39	(70)
Parity	0	7	(13)
	1 to 2	13	(24)
	3 to 4	11	(20)
	>4	22	(40)
	missing	2	(4)
Ever used contraceptive	Yes	20	(36)
	No	20	(36)
	Missing	15	(27)
Contraceptive type ever used (n=18)	Hormonal	17	(85)
	Non hormonal	1	(10)
	Missing	1	(5)
Age at Menarche (n=27)	Median, (IQR)	14, (13-15)	
Age at Menopause (n=5)	Median, (IQR)	47, (45-50)	

Clinical presentation

Abdominal pain (86%)(47/55) and abdominal distension (78%) (43/55) were the most common symptoms followed by vaginal bleeding in 40% (22/55). There were no patients with signs and symptoms of excessive androgens or of precocity (Table 4).

A pelvic mass was the most common exam finding in 55% (30/55) followed by abdominal mass in 42% (23/55). Ascites occurred in 7% (4/55) while chest signs (cough, pain), abdominal tenderness and limb oedema were rare. Pallor was documented in only 24% (13/55) (Table 4). Patients often would present with more than one symptom or sign.

Table 4. Clinical presentation of patients with primary ovarian sex cord-stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

VARIABLES		n=55*	%
Symptoms	Abdominal pain	47	(86)
	Abdominal distension	43	(78)
	Vaginal bleeding	22	(40)
	Estrogenic features	2	(4)
	Androgenic features	0	(0)
	Reduced appetite	6	(11)
	Bloating	4	(7)
	Weight loss	3	(6)
Clinical signs	Pallor	13	(24)
	Pelvic mass	30	(55)
	Abdominal mass	23	(42)
	Ascites	4	(7)
	Chest signs(cough, pain)	1	(2)
	Abdominal distension	6	(11)
	Tender abdomen	1	(2)
	Limb oedema	1	(2)
***a patient can present with more than one clinical finding**			

Investigations

Laboratory

Almost all patients (39/55) had a CA125 test done while over a third had Estradiol levels investigated. Inhibin testing was done in only 10% (5/55) and AMH in only 4% (2/55). Only 5 patients had HIV tests done and one was positive (Table 5).

Imaging

A majority of patient 84% (46/55) had Ultrasound as imaging modality. More than half of the patients (58%) (32/55) had CT-scan done while 16% (9/55) had MRI done. Only a quarter (26%) (14/55) had Chest X-rays done. No patient had a PET scan done (Table 5).

Table 5. Laboratory Investigations and imaging among patients with primary ovarian sex cord-stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

VARIABLES		n	(%)
Lab investigations n=55*	CA125	39	(71)
	Inhibin	5	(12)
	AFP	9	(22)
	CEA	7	(17)
	Estradiol	15	(37)
	Ca19-9	3	(6)
	HIV positive	1	(2)
	HIV negative	4	(7)
	BHCG	5	(12)
	AMH	2	(4)
Imaging type n= 55*	Chest X-ray	14	(26)
	Ultrasound scan	46	(84)
	CT scan	32	(58)
	MRI scan	9	(16)
	PET scan	0	(0)
	ECG	4	(7)
	Echo	3	(6)
***a patient can have more than one lab and imaging investigation**			

Pathological characteristics

Tumour histological types

Granulosa cell tumours (GCT) were the most common accounting for 80% (44/55). Fibro-thecoma tumours were 13% (7/55) while Sertoli-Leydig cell tumours were 7% (4/55) . In the granulosa cell tumour group, adult granulosa cell tumours (AGCT) were the most common accounting for 39% (17/44), while the juvenile granulosa cell tumours (JGCT) accounted for 10% (4/44) . It was noted however that 43% of GCT were not subclassified in the histology reports. Two granulosa cell tumours were associated with endometrial hyperplasia while one was associated with endometrial carcinoma. In the Fibro-thecoma spectrum there were 4 (7%) Fibromas and 1 (2%) mixed Fibro-thecoma. There were four (7%) Sertoli-Leydig cell tumours and no cases of sclerosing stromal tumour (SST) or sex cord tumour with annular tubules (SCTAT) (Table 6).

Tumour grading

Most (82%)(39/48) had no grading in the histopathology reports. Tumour grading was reported in only 9. Four were grade 1, 1 grade 2 and 4 grade 3. (Table 6).

Surgical staging

Most patients (55%)(30/55), had no documented information on surgical staging. Among those staged majority (68%)(17/25), stage 1. Only 13 patients had ascitic fluid cytology of which 5 (38%) were positive while in 31% (4/13), the cytology finding was not stated (Table 6).

Table 6: Pathological characteristics among patients with primary ovarian sex cord-stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

Variables		n	(%)
Histology class (n = 55)	Granulosa cell tumour	44	(80)
	Fibroma-Thecoma tumour	7	(13)
	Sertoli-Leydig cell tumour	4	(7)
	Other Sex cord tumours	0	(0)
GCT sub class (n = 44)	Adult GCT	17	(39)
	Juvenile GCT	4	(9)
	GCT not subclassified	23	(52)
GCT + other pathology (n=4)	Endometrial cancer	1	(2)
	Endometrial hyperplasia	2	(4)
Tumour grade n=48	Grade 1	4	(8)
	Grade 2	1	(2)
	Grade 3	4	(8)
	Not graded	39	(82)
surgical stage n=55	1	17	(31)
	2	1	(2)
	3	3	(5)
	4	4	(7)
	missing	30	(55)
ascitic fluid cytology n=13	negative	4	(31)
	positive	5	(38)
	not stated	4	(31)

Management given

All the 55 patients had surgery performed. Sixty nine percent (69%)(38/55), had adjuvant chemotherapy. Thirteen percent (13%) (7/55) did not get chemotherapy but did not require it. Eighteen percent (18%)(17/25) needed adjuvant chemotherapy but did not receive it. No patient received neoadjuvant chemotherapy, chemotherapy only, radiotherapy or palliative care (Table 7).

Surgery performed

A majority 49% had TAH+BSO while 18 % had TAH + BSO + Omentectomy. One patient had bilateral oophorectomy and one had cytoreduction. Seventy percent (39/55) had Non-fertility sparing surgery while only 16 (29%) had fertility sparing surgery. (Table 7).

Chemotherapy

Almost 70% (38/55) of patients received adjuvant chemotherapy. Bleomycin, Etoposide and Cisplatin (BEP) was the most common first line combination in 82% (31/55) of patients. Cisplatin with Paclitaxel was the commonest combination as second line chemotherapy given to 2 of the five patients who required second line. Seventy four percent (74%)(32/43) of patients received 4 to 6 cycle of chemotherapy. (Table 7)

Table 7: Management given to patients with primary ovarian sex cord stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

Variables		N=55	%
Management given n = 55	Surgery	55	(100)
	Adjuvant Chemotherapy given	38	(69)
	Adjuvant Chemo not required	7	(13)
	Adjuvant Chemo missed	10	(18)
	Chemotherapy only	0	(0)
	Neoadjuvant Chemotherapy	0	(0)
	Radiotherapy	0	(0)
	Palliative care	0	(0)
Surgery performed n=55	Unilateral oophorectomy	16	(29)
	Bilateral oophorectomy	1	(2)
	TAH+BSO	27	(49)
	TAH+BSO+Omentectomy	10	(18)
	Exploratoty laparotomy +biopsy	0	(0)
	Cytoreduction	1	(2)
Chemo status	Not documented	10	(18)
	Not given	7	(13)
	1st line	38	(69)
	2nd line	5	(13)
First Line n=38	Bleomycin, Etoposide, Cisplatin (BEP)	31	(82)
	Cisplatin, Paclitaxel	5	(13)
	Cisplatin, Cyclophosphamide, Actinomycn D	1	(3)
	Cisplatin, Cyclophosphamide, Vincristine	1	(3)
Second Line n=5	Cisplatin,Paclitaxel	2	(40)
	Paclitaxel.Gemcitabine	1	(20)
	Vincristine,Cyclophosphamide	1	(20)
	Vincristine,Cyclophosphamide,Actinomycn D	1	(20)
Number of chemo cycles n=43	< 4	5	(11)
	4 to 6	32	(74)
	> 6	6	(14)

Management outcomes overall

Information on patient status at 2 and 5 yrs was not available in some files. Phone call inquiries with oral consent were made to get information using contacts in the patient files.

Treatment outcomes were good. Over 73% (33/45) of patients were alive at two years since diagnosis while about 11% (5/45) had died. There was no information on 7 patients representing 15.6%. There were no cases of tumour persistence or recurrence at two years following management.

Over 56% (15/27) of patients were alive five years after management while 2 patients still alive had had tumor recurrences. Whereas there were no documented additional deaths, there was no information on status of the patients among 18.5% (5/27) of patients (Table 8)**.**

Table 8: Management outcomes overall among patients with primary ovarian sex cord - stromal tumours managed at Kenyatta National Hospital from 2010 to 2020

Period	Status	n	(%)
At 2 years n=45	Alive	33	(73.3)
	Recurred	0	(0)
	Persisted	0	(0)
	Died	5	(11.1)
	Missing	7	(15.6)
At 5 years n=27	Alive	15	(55.6)
	Recurred	2	(7.4)
	Persisted	0	(0)
	Died	5	(18.5)
	Missing	5	(18.5)

Management outcome relative to age

At 2 years 73.9% (17/23) of those below 50 years were alive compared to 72.0% (16/22) over 50 years. There were no tumour recurrences in both groups (Table 9).

At 5 years 60% (9/15) of those below 50 years were alive compared to 50% (6/12) over 50 years. There was one recurrence each in the under 50 and in the over 50 years (Table 10).

Management outcome relative to surgery performed

At 2 years 92.3% of those who underwent FSS were alive while for Non-FSS 65.6% were alive. There were no recurrences in the two groups. (Table 9).

At 5 years 88.9% (8/9) of patients after FSS were alive compared to 38.9% (7/18) for Non-FSS. No patient after FSS and 11.1% (2/18) after Non-FSS had recurrence. At five years there were 1 death in the FSS and 4 in the non-FSS group (Table 10).

Management outcome relative to administration of adjuvant chemotherapy

Among patients who received adjuvant chemotherapy 75.8% (25/33) were alive at 2 years and there was no tumour recurrence. Among those who did not receive adjuvant chemotherapy 83.3% (5/6)were alive at 2 years and there was no tumour recurrence. In 6 patients it was not clear from the records whether they received adjuvant chemotherapy or not but 3 were alive. They could not be reached by phone (Table 9).

Among patients who received adjuvant chemotherapy 57.9% (11/19) were alive at 5 years and there were 2 tumour recurrences. Among those who did not receive adjuvant chemotherapy 75% (3/4) were alive at five years and there was no tumour recurrence. In 4 patients it was not clear from the records whether they received adjuvant chemotherapy or not and whereas 2 of them had died, 2 could not be reached by phone (Table 10).

Management outcome relative to stage of disease

Only 17 (31%) of patients had the disease staged. Of those staged 11 (64.7%) were in Stage 1 and 6 (35.3%) had stage higher than Stage 1. For those at stage 1, 100% were alive and there were no recurrences at 2 years. Only 16.7% of patients at stage higher than stage 1 were alive at 2 years. Among those not staged 75% were alive at 2 years (Table 9).

For those at stage 1, 100% were alive and there were no recurrences at 5 years. None of the patients at stage higher than stage 1 were alive at 5 years. Among those not staged 53.3% were alive at 5 years and 13.3% recurred (Table 10).

Management outcome relative to histology type

Among patients with GCT 71.4% (25/35)were alive at 2 years. One hundred percent of the patients with Fibro-thecoma tumours were alive at 2 years. Only 50% (2/4) of patients with Sertoli-Leydig tumours were alive at 2 years. There were no recurrences in all groups at 2 years (Table 9).

Among patients with GCT 47.4% (9/19) were alive at 5 years. 100% (9/9) of the patients with Fibro-thecoma tumours and 50% (2/4) of patients with Sertoli-Leydig tumours were alive at 5 years. Of those with GCT 10.5% (2/9) had recurrences at 5 years (Table 10).

Table 9: Management outcome at 2 years relative to age, surgery type, adjuvant chemo, disease stage and histological type among patients with primary ovarian sex cord-stromal tumours managed at Kenyatta National Hospital from 2010 to 2020.

Variables		Alive	Recurred	Died	Missing
		n (%)	n (%)	n (%)	n (%)
Age at diagnosis	<50 yrs n=23	17 (73.9)	0 (0)	3 (13)	3 (13)
	≥50 yrs n=22	16 (72)	0 (0)	2 (9.1)	4 (18.2)
Surgery type	FSS n=13	12 (92.3)	0 (0)	1 (7.7)	0 (0)
	Non-FSS n=32	21 (65.6)	0 (0)	4 (12.5)	7 (21.9)
Adjuvant chemo	ACT given n=33	25 (75.8)	0 (0)	2 (6.1)	6 (18.3)
	ACT not given n=6	5 (83.3)	0 (0)	1 (16.7)	0 (0)
	ACT no info n=6	3 (50)	0 (0)	2 (33.3)	1 (16.7)
Disease stage	Stage 1 n=11	11 (100)	0 (0)	0 (0)	0 (0)
	Stage >1 n=6	1 (16.7)	0 (0)	5 (83.3)	0 (0)
	Not staged n=28	21 (75)	0 (0)	0 (0)	7 (25)
Histological type	Granulosa cell n=35	25 (71.4)	0 (0)	4 (11.4)	6 (17.1)
	Fibro-thecoma n=6	6 (100)	0 (0)	0 (0)	0 (0)
	Sertoli-Leydig n=4	2 (50)	0 (0)	1 (25)	1 (25)

FSS : Unilateral Salpingoophorectomy, Non-FSS: TAH + BSO, TAH + BSO + omentectomy

Table 10: Management outcome at 5 years relative to age, surgery type, adjuvant chemo, disease stage and histological type among patients with primary ovarian sex cor- stromal tumours managed at Kenyatta National Hospital from 2010 to 2020.

Variables		Alive	Recurred	Died	Missing
		n (%)	n (%)	n (%)	n (%)
Age at diagnosis	<50 yrs n=15	9 (60)	1 (6.7)	3 (20)	2 (13.3)
	≥50 yrs n=12	6 (49.8)	1 (8.3)	2 (16.6)	3 (24.9)
Surgery type	FSS n=9	8 (88.9)	0(0)	1 (11.1)	0 (0)
	Non-FSS n=18	7 (38.9)	2 (11.1)	4 (22.2)	5 (27.8)
Adjuvant chemo	ACT given n=19	11 57.9)	2 (10.5)	2 (10.5)	4 (21)
	ACT not given n=4	3 (75)	0 (0)	1 (25)	0 (0)
	ACT no info n=4	1 (25)	0 (0)	2 (50)	1 (25)
Disease stage	Stage 1 n=7	7 (100)	0 (0)	0 (0)	0 (0)
	Stage >1 n=5	0 (0)	0 (0)	5 (100)	0 (0)
	Not staged n=15	8 (53.3)	2 (13.3)	0 (0)	5 (33.3)
Histological type	Granulosa cell n=19	9 (47.4)	2 (10.5)	4 (21)	4 (21)
	Fibro-thecoma n=4	4 (100)	0 (0)	0 (0)	0 (0)
	Sertoli-Leydig n=4	2 (50)	0 (0)	1 (25)	1 (25)

DISCUSSION:

Out of 1296 patients with ovarian tumours identified in the study, 55 had confirmed SCSTs representing 4.2%. The median age was 46 years. Granulosa cell tumours (GCT) accounted for 80% (44), Fibro-thecomas 13% and Sertoli-Leydig cell tumours were 7%. Of the GCT adult granulosa cell tumours (AGCT) were the commonest accounting for 39%, while juvenile granulosa cell tumour (JGCT) accounted for 9% and 52% were not sub-classified. Abdominal pain (86%) and abdominal distension (78%) were the most common symptoms while vaginal bleeding was found in 40%. A pelvic mass was palpable in 55% of the patients. All patients underwent surgery out of which only 32% were fertility sparing surgery (FSS). Information on tumor staging and grading was poorly documented but most (33%) were stage 1 and (40%) grade 1. BEP was the most used adjuvant chemotherapy regime. Seventy three percent were alive at 2 years and 55.6% at 5 years. Recurrence was noted in 7.4% at 5 years**.**

In the study we found that SCSTs make up 4.2% of all ovarian neoplasms which is slightly lower than the global average of 5-8% (7) but similar to rates of 4% reported in Pakistan Studies(3, 8).

Granulosa cell tumours (GCTs) are the most common SCST subtype as was found in 80% in the study. This is comparable with other studies in Pakistan, Ghana and Egypt (3, 8, 10). Among the GCTs Adult GCT made up 39% of the case while Juvenile GCT were 9%. Similar studies have showed majority of GCTs are adult type. They were reported to make up 95% in Germany (16), 90.0% in the United States of America (USA) (17), 92% in Pakistan (3, 8) and 85.2% in Tehran (10). Our percentage was much lower than reported but it is noted that in our study 52% of the histopathology reports did not subclassify the GCT into either Adult GCTs or Juvenile GCT.

In this study tumours in the fibroma-thecoma group made up 13% and Sertoli-Leydig cell tumours made up 7% of the SCSTs. In literature they are reported to be rare. In other studies Fibromas make up about 4%, Theca cell tumours 0.5-1% and Sertoli-Leydig cell tumours 0.5-1% of all neoplasms (6, 9, 14). The higher rate in this study could be because we looked at all SCSTs while some studies analyse only malignant SCSTs therefore report much lower rates in these subtypes. In the USA a rate of 10.0% in the USA was reported and Less than 5% are malignant (3, 8, 17).

Though reported elsewhere (6, 9, 14), other SCST subtypes like Sclerosing SCST and SCST with Annular tubules were not reported in this study. These are rare therefore we needed a much larger sample size to get some.

The age range reported in this study of 7 years to 81 years, reflects what has been documented in other populations. For instance, SCSTS have been reported between 4-93 years in the USA (17), 1-92 years in Pakistan (3, 8), 16-76 years in Ghana (10), 13-84 years in Egypt (15) and 4 to 70 years in India (22). Majority of SCSTs however tend to present in younger patients as was reported in this study. Most (36%) participants were in the 25 to 45 age group with 13% younger than 24 years with median age at presentation being 46 years. This compare with other studies which have reported median age of presentation as 45 years in Pakistan (3, 8), 41 years in Tehran (23), 47 years in Egypt (15), 40 years in Ghana (10) and 51 years in the USA (20), Other studies reported that of SCSTs 12% are younger than 30 years and 57% are between ages 30 to 59 years (17). In a study in the USA 50% of patients were less than 50 years (20).

Eighty six percent presented with abdominal pain and 78% with abdominal distension while 55% had pelvic masses on examination. The findings were similar to other studies. Studies show that SCSTs have diverse clinical features like a pelvic or abdominal mass, pain, discomfort, abdominal swelling and gastrointestinal symptoms (6, 14, 17). In Pakistan a mass and pain was found in 67% and distension in 54% of cases (3, 8). In India a mass and pain made up 51.3% of the presentation (4) while in Egypt abdominal pain was found in 54.5% and a mass in 53.2% of cases (15).

Even though it is reported that large tumours may undergo torsion or rupture, resulting in an acute presentation with pain and haemoperitoneum (6, 14, 17), none of our patients presented as an acute emergency

None of the patients presented with features of precocious puberty or virilisation. It is reported that 30-50% of all SLCTs produce androgens and are the most common virilizing ovarian tumour, occurring in more than 33% of cases (6, 9, 14). SLCTs are rare, we needed a high sample size to have virilization as a feature.

Cases of GCT accompanied with endometrial hyperplasia was found in 2 cases (4%) and endometrial cancer in 1 case (2%). None of the patients had undergone endometrial sampling preoperatively. This has been reported elsewhere and some recommend endometrial sampling to rule out endometrial cancer co-existing with the SCST.

Fourty percent of the patients presented with abnormal vaginal bleeding. In a study in India, 31% of patients had abnormal menses (4). In Pakistan menstrual abnormalities were common but hormonal changes were rare (3, 8), while in Egypt menstrual abnormalities were associated with GCT (15). 40% of patients in our study presented with abnormal ars had precocious puberty (22).

Confirmation of SCST relied on histology reporting with no immunohystochemistry (IHC) done to any of the specimen though IHC with Inhibin and FOXL2 improved accuracy in studies Pakistan and India (3, 8, 17, 18, 19).

The most common tumor marker assayed in our study was CA-125 in almost all patients (91%), while 37% had Estradiol levels investigated. Inhibin testing was done in only 12% and AMH in only 4%. AFP, CEA, Ca19-9 and BHCG were also tested for some patients but Serum calcium levels were not tested in any. In a study in Egypt 55.8% had elevated CA-125 (15). In a study by Dimitrios in early stage disease, elevated preoperative CA-125 levels were associated with worse outcomes (24). Our study did not quantify CA125 levels. Even though Inhibin is a better marker it is more costly and less available hence most patients end up with CA125 which is not a good marker for SCSTs.

A majority of our patients (84%) had Ultrasound as imaging modality. More than half of the patients (58%) had CT-scan done while 16% had MRI done. Only a quarter (26%) had Chest X-rays done. No patient had a PET scan done. In a study in Egypt imaging was able to pick up all masses (15). Ultrasound scans unlike other imaging modalities are available and often affordable.

Among the patients 31% were diagnosed at Stage 1. It was noted however that in 55% of the cases the stage was not documented. In literature most malignant SCSTs are confined to the ovary in 57% of women. Patients are often diagnosed at early stage. In the study only 17 (31%) of patients had staging but of those staged 11 (64.7%) were in Stage 1 and 8 (35.3%) had stage higher than Stage 1. In a study in Egypt 95% had early disease (64.5% stage 1) (15) while in the USA 81.0% had early disease (70.5% stage 1, 10% stage II) (20). In Tehran

87.1 % were in stage I (23). In the present study only 38% of patients were staged but among those 61.9% presented at stage 1. The percentage was low because most were not staged.

Malignant SCSTs may be well-differentiated or less well differentiated on histology but most present as low-grade disease (6,9,14,17, 20). In the study 82% of the histology had no tumor grading in the report. Only 10 were graded of which 4 were grade 1, 2 were grade 2 and 4 were grade 3. No meaningful analysis could be made.

Surgery is the primary treatment for SCSTs and outcomes are favourable. Surgical notes should clearly state whether there was any rupture of the ovarian capsule and tumor seeding (5, 26, 27, 28). All the patients in the study underwent surgery for diagnosis and management but staging was adequately documented in only 45% of cases.

Surgery may be fertility sparing surgery (FSS) or non fertility sparing surgery (Non-FSS) (5, 12, 16, 26, 30). In the study 67% had Non-FSS while 32% had FSS. In USA studies 34% of patients underwent FSS (20), 40% in Tehran (23), 23% in Italy (26) and 30% in Egypt (15). The rates of FSS are comparable to the USA and Egypt.

In this study no case of bilateral ovarian SCSTs was reported in the intraoperative notes and the histopathology reports. In literature SCST usually involve 1 ovary and only in 2-8% are both ovaries involved (3, 6, 14).

None of the patients underwent lymph node dissection (LND). Routine LND can be omitted in SCST as there is a very low risk of metastasis to the nodes. Enlarged nodes picked on imaging or encountered during surgery should however be dissected. In a study by Dimitrios LND was performed in 49.5% but metastases were present in only 3.3%. (5, 26, 27, 28, 29).

Almost 70% of patients received adjuvant chemotherapy (ACT). For 1st line chemotherapy 82% received Bleomycin, Etoposide and Cisplatin (BEP) while 13% received Carboplatin and Paclitaxel. In an Egyptian study 46.7% of their patients got ACT, while in the USA they were 51.9% and 35% in an Italian study. In most studies standard ACT involves BEP while Paclitaxel and Carboplatin been found to be as active but less toxic. Indications for adjuvant CT include Stage II–IV disease and Stage I disease with a big tumour size, high mitotis, high-grade histology, SLCT tumour subtype, tumour rupture and incomplete surgical staging. (5, 12, 15 20, 21, 26, 30, 31, 32, 33). There were no obvious criteria for initiation of or choice of chemotherapy in this study and this could explain the high ACT use rate.

None of the patients was treated with radiotherapy. Even though the place for radiation therapy (RT) remains controversial GCT are radiosensitive and radiotherapy has been used for local advanced stage or local recurrent disease. In a study in the USA 2.1% got RT (20) while in Tehran 9.7% received RT (23). Zhagalo found in Italy 35% needed chemotherapy and RT (26). Most of the patients in the current study had early stage disease and had a low tumor recurrence rate.

In this study we had no recurrences at 2 years and had two recurrences at 5 years which is 7.4% rate. Studies show recurrences in most patients happens within the first few years and relapse with stage IC disease can be as high as 30-40%. Relapse with adult GCT may take more than 10 years while with Juvenile GCT most frequently recur within the first few years (5, 12, 16, 26, 30). In a study in Egypt metastasis/recurrence was found among 20% of their patients (15). Our recurrence rate was low but this was only at 5 years. A longer follow-up period would be more informative.

Treatment outcome of SCSTs is favourable because most patients present in early stage and the tumours are chemosensitive. In a German population based study of survival they reported a 5 year overall survival (OS) of 89.1% and a 10 year OS of 78.3% for women diagnosed after 1988. Factors that influence survival include Patient age, FIGO Stage, histological subtype, rupture of capsule, tumour differentiation, residual tumour after surgery and recurrence (5, 16, 26, 35).

Overall we had 10 deaths among the 45 patients analysed. Five were dead at 2 years and another 5 at 5 years. Survival analysis in our study was limited by the small numbers and loss to follow-up. Some information on patients lost to follow up was made by phone calls after verbal consent utilising the last telephone contacts in the file.

Age less than or equal to 50 years improves overall survival. In the study at 2 years 73.69% of those below 50 years were alive compared to 72.0% of those 50 years and above. There were no tumour recurrences in both groups. At 5 years 60% of those below 50 years were alive compared to 49.8% of those 50 years and over. There was a 6.7% recurrence in the under 50 and an 8.3% recurrences in those 50 years and over. In studies on early disease in Germany, patient age less than 50 years had survival rates 93% while those aged over 50 years had survival rates 84% in Germany (16). In the USA survival for those aged less than 50 years was 97% while that for those aged over 50 years was 92%. Patients younger than 50 years were noted to have a 10 year survival that was better than those more than 50 years (81% compared to 64%) (20). In our study survival aged less than 50 years was slightly better than after age 50 years. Our survival rates were lower than in the USA probably due to different demographics and healthcare system issues.

FIGO stage influences survival. Disease at an early stage is a significant factor that improves overall survival (16, 20). Five year survival rates for early stage disease have been reported as 90-95% (21, 24) while in late stage disease 5 year survival is 25-59% (20). In the study for those at stage 1, all were alive and there were no recurrences at 2 and 5 years. Only 16.7% of patients at stage higher than stage 1 were alive at 2 years.

The type of Surgery has no effect on survival in early stage disease. In the study at 2 years 92.3% of those who underwent FSS were alive while for non-FSS 65.6% were alive. There were no recurrences in the two groups. At 5 years 88.9% of patients after FSS were alive compared to 38.9% for non-FSS. No patient after FSS had recurrence while 11.1% after non-FSS had recurrence. At five years there were 11.1% deaths in the FSS and 22.2% in the non-FSS group. Among patients undergoing fertility sparing surgery in the USA, Mallory reported survival for stage I-II of 94.8% while survival for stage I-II after non-fertility sparing surgery was 94.9%. FSS is a safe alternative in these young patients (20, 23). Among the study patients FSS did not seem to have an adverse effect on the outcome.

Performance of pelvic LND has no difference on overall survival (20). There was no documentation on lymph node status or lymph node dissection among our patients.

Among patients who received adjuvant chemotherapy 75.8% were alive at 2 years and there was no tumour recurrence. Among those who did not receive adjuvant chemotherapy 83.3% were alive at 2 years and there was no tumour recurrence. In 6 patients it was not clear from the records whether they received adjuvant chemotherapy or not but 50% were alive. They could not be reached by phone. Among patients who received adjuvant chemotherapy 57.9% were alive at 5 years and there was a 10.5% tumour recurrence. Among those who did not receive adjuvant chemotherapy 75% were alive at five years and there was no tumour

recurrence. In 10 patients it was not clear from the records whether they received adjuvant chemotherapy or not and whereas 50% of them had died, 25% were alive but could not be reached by phone. Our findings are similar to studies in the USA and Germany that show adjuvant chemotherapy has no difference on overall survival (16, 20).

Survival is 100% if well differentiated and 77.8% if moderately and poorly differentiated. In a study at AKUH Pakistan on SLCT only 8.8% were well differentiated and 44.1% were intermediate (3, 8). In the USA 5 year survival with Grade 1-2 tumour was 96% while with Grade 3 was 64%. In the same study the 10 year survival with Grade 1-2 tumour was 86% while with Grade 3 tumour it was 59% (20). No meaningful analysis could be made on survival in the study due to missing grading in most reports.

Tumour Subtype has influence on survival. In the study 71.4% with GCT all the patients with Fibro-thecoma tumours and only 50% of patients with Sertoli-Leydig tumours were alive at 2 years. There were no recurrences in all groups at 2 years. Fourty seven with GCT 100% with Fibro-thecoma tumours and 50% with Sertoli-Leydig tumours were alive at 5 years. Of those with GCT 10.5% had recurrences at 5 years. With GCT, studies report 5 year survival rate exceed 90%. Mortality with juvenile GCT is only 1.5% with stage IA (20). Theca cell tumours and Fibromas are often benign and therefore their 5year survival is nearly 100% as seen in our study. With Sertoli-Leydig cell tumours (SLCT), 5 year survival is 92.3% for FIGO stage I and 33.3% if more than stage 1. Survival is 100% if well differentiated and 77.8% if moderately and poorly differentiated. In a study at AKUH Pakistan on SLCT only 8.8% were well differentiated and 44.1% were intermediate (3, 8). Most patients presented at FIGO Stage 2 or higher.In a study in Egypt DFS was 50.5 months and OS was 49.5 months among patients with SLCT (15).

STUDY STRENGTHS

This is the first local study specifically focusing on SCSTs. This study was able to review cases of SCSTs of ovary and establish baseline data on various aspects of clinico-patholigical presentation, management and management outcomes that future bigger studies can build on. All the 55 files of patients with histologically confirmed SCSTs were analysed and all available data included in the study. Calls were made to find out the status of patients lost to follow-up.

STUDY LIMITATIONS

Our study was not without limitations. In view of the retrospective nature of the study missing files and missing information in available files were a major study limitation. This was minimized by aiming for a high file retrieval rate doing multiple file searches**,** including all files with histology results and analysing all variables where data was available in the files. There were deficiencies in health infrastructure and recording of health statistics which could have affected ICD10 coding of the tumours and hence some could have been missed. This was minimised by including searches with codes C56, D39.1 and D27 to increase identification. It was difficult to tell the outcome of patients lost to follow yet lifelong follow up is recommended. Most patients do not continue with long follow-up yet this is critical in SCSTs since these tumours are indolent and recurrence may manifest after many years. Information was improved by making telephone calls utilising the contact numbers in the file.In our study the cases were few hence the study was not powered enough for good statistical analysis.

Our study could have been affected by selection bias based on missing data and we couldn't compare FSS and non FSS, because characteristics may not have been similar. Our findings may therefore not be generalized to other populations.

CONCLUSIONS

Patients presented at a wide age range from 7-81 years. Majority of our patients are young, most in their reproductive years. Most patients present at early stage. The most common clinical signs and symptoms were abdominal pain, abdominal distension while on physical examination the commonest signs were abdominal mass and distension. Most patients were not staged. All patients had surgery, some had chemotherapy. Only 31% had FSS. Management outcomes were good at 2 years and 5 years. Patient age, tumor stage and tumour histological type influence outcome at 2 and 5 year. Some files could not be traced and some of the files lacked critical details

RECOMMENDATIONS

There is need to develop and implement clear guidelines/protocols on treatment and follow up of patients with SCSTs. Patient notes recording, documentation, record keeping, data capture and filing should be improved. This will entail the creation of a template for patient clerkships to capture all important information and development of a robust cancer registry with a software based database for ease of information access that will help in data collection, collation and analysis. Introduction of a standardised electronic medical record system for the oncology unit where the various service delivery points capture data that is fed directly into a central server will minimise errors and omissions

A multidisciplinary team (MDT) team that includes discussions with pathologists and imaging staff should be formed to improve on reporting on SCSTs. Improvement on imaging

and reporting can narrow down differentials while better reporting on tumours subtypes and grading will improve care.

There need to be improvements on our surgical approach so that surgical staging and procedures performed are standardised and well documented as they affect treatment, outcome and follow-up.

There is need to create a follow-up and monitoring structure that encourage patients to continue long term follow up to minimize loss to follow up to catch recurrences early and ensure long term survival.

Further multicenter studies on to be conducted including all major hospitals with gynecological oncology services to increase the sample size to better understand SCSTs inour population.

RESULTS DISSEMINATION

The research findings will be presented to the divisions of obstetrics and gynaecology UON and KNH to help inform development of policy and management guidelines for SCSTs and a report made to KNH/UON Ethics and Research Committee. The work will be published in a peer-reviewed journal.

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Table 11 - TIMELINES

Activity	2020										2021
	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Proposal Development											
Ethical approval and											
Seeking for funding											
Data collection											
Data analysis											
Report writing											
Presentation of results											
Final Dissertation											

Table 12 - BUDGET

ITEM	UNITS		COST	TOTAL (KSH)
Personnel				
Research assistant	2	1,000Shs per day for 10 days each	10,000.00	20,000.00
Stastician	1		50,000.00	50,000.00
Sub total				**70,000.00**
Printing				6,000.00
Questionnaires	1	3 pages each	20.00	60.00
Final report	1	100 pages each	20.00	2,000.00
Sub total				**8,060.00**
Photocopy				
Questionnaire	3	100 copies each	2.00	600.00
Final report	4	100 copies each	2.00	800.00
Final report binding	4		200.00	800.00
Sub total				**2,200.00**
Other Costs				
ERC Fees	1		2.000	2,000.00
Phone calls	100		50.00	200.00
Sub - total				**2,200.00**
GRAND TOTAL				**86,060.00**

CHAPTER 6: APPENDICES

APPENDIX 1: WHO classification of Ovarian Stromal Tumours (2014 revision)

Table 1. WHO classification scheme for ovarian sex cord-stromal tumors (2014)

Pure stromal tumors

- Fibroma
- Cellular fibroma
- Thecoma
- Luteinized thecoma associated with sclerosing peritonitis
- Fibrosarcoma
- Sclerosing stromal tumor
- Signet-ring stromal tumor
- Microcystic stromal tumor
- Leydig cell tumor
- Steroid cell tumor
- Steroid cell tumor, malignant

Pure sex cord tumors

- Adult granulosa cell tumor
- Juvenile granulosa cell tumor
- Sertoli cell tumor
- Sex cord tumor with annular tubules

Mixed sex cord-stromal tumors

- Sertoli-Leydig cell tumors
  - Well-differentiated
  - Moderately differentiated with heterologous elements
  - Poorly differentiated with heterologous elements
  - Retiform with heterologous elements
- Sex cord-stromal tumours, NOS*

WHO, World Health Organization; NOS, not otherwise specified.

APPENDIX 2: FIGO Staging for Ovarian Cancer

Surgical FIGO - Ovarian Cancer Staging 1988		Surgical FIGO - Ovarian Cancer Staging 2014	
I	Tumors limited to one or both ovaries	I	Tumor confined to ovaries or fallopian tubes
IA	Tumor limited to one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites/peritoneal washings	IA	Tumor limited to one ovary, capsule intact or fallopian tube, no tumor on ovarian or fallopian tube surface, no malignant cells in ascites or peritoneal washings
IB	Tumor limited to both ovaries; capsule intact; no tumor on ovarian surface; no malignant cells in ascites/peritoneal washings	IB	Tumor involves both ovaries; capsule intact or fallopian tubes, no malignant cells in ascites or peritoneal washings
IC	Tumor limited to ovaries with any of the following: capsule ruptured, tumor on ovarian surface, positive washings/ascites	IC1-3	Tumor limited to one or both ovaries/fallopian tubes IC1: Surgical spill intraoperatively IC2: Capsule rupture before surgery or tumor on ovarian or fallopian tube surface IC3: Malignant cells in the ascites or peritoneal washings
II	Tumor involves one or both ovaries with pelvic extension or implants	II	Tumor involves one or both ovaries or fallopian tube with pelvic extension (below the pelvic brim) or primary peritoneal cancer
IIA	Extension and/or implants on uterus or fallopian tube; negative washings/ascites	IIA	Extension and/or implants on uterus and/or fallopian tubes
IIB	Extension or implants onto other pelvic structures; negative washings/ascites	IIB	Extension to other pelvic intraperitoneal tissues
IIC	Pelvic extension (IIA or IIB) or implants with positive peritoneal washings/ascites		
III	Microscopic peritoneal implants outside of the pelvis; or limited to the pelvis with extension to the small bowel or omentum	III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	Microscopic peritoneal metastases beyond pelvis	IIIA	IIIA1: Positive retroperitoneal lymph nodes only IIIA1(i): Metastasis ≤ 10 mm IIIA1(ii): Metastasis > 10 mm IIIA2: Microscopic, extrapelvic (above the pelvic brim) peritoneal involvement ± positive retroperitoneal lymph nodes
IIIB	Macroscopic peritoneal metastases beyond pelvis < 2 cm in size	IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
IIIC	Macroscopic peritoneal metastases beyond pelvis > 2 cm and/or positive retroperitoneal or inguinal lymph nodes (pT3B N1 or pT3C)	IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen (no parenchymal involvement).
IV	Distant metastasis including pleural effusion with positive cytology. Distant metastases outside the peritoneal cavity. Parenchymal liver/splenic metastasis.	IV	Distant metastasis excluding peritoneal metastasis
		IVA	Pleural effusion with positive cytology/biopsy
		IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)
			Bowel infiltration-transmural with mucosal involvement, umbilical deposit

Source: Dennis S. Chi, Andrew Berchuck, Don S. Dizon MD, Catheryn Yashar , Chapter 25 Ovarian Sex Cord-Stromal Tumours, Principals and Practice of Gynecologic Oncology, Philadelphia, PA : Elsevier, 2017, 7th edition Pages 725–739

APPENDIX 3: **DATA ABSTRACTION FORM**

Study No:_____ **Date:**_____

1. SOCIAL DEMOGRAPHIC DATA

Patient Age at diagnosis in Years_____Date of diagnosis in _____

Marital status

a) Single[ ] b) Married[ ] c) Separated[ ] d) Widowed[ ] e) Not stated[ ]

Highest level of education

a) Primary[ ] b) Secondary[ ] c) Tertiary[ ]d) None[ ] e) Not stated[ ]

Employment status:

a) Formal employement[ ] b) Self Employed[ ] c) Not Employed[ ] e) Not stated[ ]

2. OBSTETRICS AND GYNAECOLOGY HISTORY

Parity

a) 0 [ ] b) 1- 2 [ ] c) 3 - 4 [ ] d) >4 [ ] e) Not stated[ ]

Contraceptive use

a) Yes [ ] b) No [ ] c) Not stated[ ] If yes specify:_____

Age at Menarche a)___Yrs b) Not stated[ ] Age at Menopause a)___Yrs b) Not stated[ ]

3. CLINICAL PRESENTATION

a) Abdominal pain	Yes [ ]	No [ ]	
b) Abdominal distension	Yes [ ]	No [ ]	
c) Vaginal bleeding	Yes [ ]	No [ ]	
d) Estrogenic features	Yes [ ]	No [ ]	If Yes Specify_____
e) Androgenic features	Yes [ ]	No [ ]	If Yes Specify_____
f) Others:	[ ] Specify_____		

4. PHYSICAL EXAMINATION

Pallor	Yes [ ]	No [ ]	
Pelvic mass	Yes [ ]	No [ ]	
Abdominal mass	Yes [ ]	No [ ]	
Ascites	Yes [ ]	No [ ]	
Abdominal distension	Yes [ ]	No [ ]	
Chest signs	Yes [ ]	No [ ]	If Yes Specify_____

Others: [ ] Specify_____

5. INVESTIGATION

Laboratory

a) CA125 Yes [ ] No [ ] Lab value_____
d) Inhibin Yes [ ] No [ ] Lab value_____
c) AFP Yes [ ] No [ ] Lab value_____
d) CEA Yes [ ] No [ ] Lab value_____
e) Estradiol Yes [ ] No [ ] Lab value_____
f) HIV test Yes [ ] No [ ] Lab results_____
f) Others: [ ] Specify_____

Imaging

a) Chest X-ray Yes [ ] No [ ]Specify abnormality_____
b) Ultrasound Yes [ ] No [ ]Specify abnormality_____
b) CT scan Yes [ ] No [ ]Specify abnormality_____
c) MRI Yes [ ] No [ ]Specify abnormality_____
d) PET Yes [ ] No [ ]Specify abnormality_____
e) Others: [ ] Specify_____

6. NEOADJUVANT CHEMOTHERAPY

Yes [ ] No [ ] If Yes indication_____

7. SURGICAL STAGE

Stage 1[ ]	1A [ ]	1B [ ]	1C [ ]
Stage 2 [ ]	2A [ ]	2B [ ]	2C [ ]
Stage 3 [ ]	3A [ ]	3B [ ]	3C [ ]
Stage 4 [ ]	4A [ ]	4B [ ]	
Not stated[ ]			

8. ASCITIC FLUID FOR CYTOLOGY

Ascitic fluid present [ ] Washout done [ ] Fluid Taken [ ] Fluid Not taken [ ]

If taken Fluid cytology Positive [ ] Negative [ ] Not stated [ ]

9. TREATMENT GIVEN

Surgery [ ] Chemotherapy [ ] Radiation [ ] Chemoradiation [ ] Palliative Care [ ]

10. TYPE OF SURGERY PERFORMED

Unilateral Oophorectomy [ ]
Bilateral Oophorectomy [ ]
TAH + BSO [ ]

TAH + BSO + Omentectomy [ ]
Exploratory lap + biopsy [ ]
Others, Specify _____

11. HISTOPATHOLOGY RESULTS

Present [ ] Not Present[ ] Histological diagnosis_____

12. TUMOUR GRADE

a) Grade 1 [ ] b) Grade 2[ ] c) Grade 3[ ] d) Not graded [ ]

13. CHEMOTHERAPY REGIMES

First line chemotherapy [ ] Specify_____

Second line chemotherapy [ ]Specify_____

Others [ ]Specify_____

Number of cycles_____

14. TREATMENT OUTCOME

AT TWO YEARS

a) Alive [ ]
b) Recurrence [ ]
c)Persistence [ ] if recurrent time from treatment to recurrence _____
d) Died [ ] if diseased time from treatment to death _____

AT FIVE YEARS

a) Alive [ ]
b) Recurrence [ ]
c) Persistence [ ] if recurrent time from treatment to recurrence _____
d) Died [ ] if diseased time from treatment to death _____

APPENDIX 4 - KNH / UON-ERC APPROVAL

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel: (254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/16

21 January 2021

Dr. Walter P. Konya
Reg. No.H117/2817/2019
(Fellowship in Gynecologic Oncology)
Dept.of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Konya

RESEARCH PROPOSAL – REVIEW OF CLINICO-PATHOLOGICAL PRESENTATION, MANAGEMENT AND OUTCOMES OF PATIENTS WITH SEX CORD-STROMAL TUMOURS OF THE OVARY MANAGED AT K.N.H FROM 2012 TO 2019 (P614/11/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 21st January 2021 – 20th January 2022.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Obstetrics and Gynaecology, UoN
Supervisors: Prof. S.B. Ojwang, Dept.of Obstetrics and Gynaecology, UoN
Dr.Gwako G.N., Dept.of Obstetrics and Gynaecology,UoN
Dr. Ondieki D.K., Dept.of Obstetrics and Gynaecology, UoN

APPENDIX 5: VERBAL TELEPHONE CALL CONSENT

ENGLISH VERSION:

PHONE CALL CONSENT
Clinico-pathological characteristics, management and outcomes of patients with primary ovarian sex cord stromal tumours managed at KNH from 2010 to 2020.
I am Dr Walter Konya, the lead researcher in a study looking Clinico-pathological characteristics, management and outcomes of patients with primary ovarian sex cord stromal tumours managed at Kenyatta National hospital KNH. This study will evaluate 96 patients cared for at KNH from 2010 to 2020, and you are one of them. Your phone number is listed in the hospital file. I am calling because I need your assistance to clarify some of the information that is missing or unclear from your file. This information will help us complete the study and understand how to manage patients with Ovarian Sex cord-stromal tumours. This study has been approved by Kenyatta National Hospital/University of Nairobi Research and Ethics Committee. The Ethics Committee has granted access to your file. None of your identifying information will be collected. Information collected will be used only for purposes of this study. Your information will be kept confidential. Please note that the call may be recorded for reference purposes.The phone call will last a maximum of five minutes. Should you choose not to give any information or stop giving information at any point, it will not affect care given to you or your loved one at Kenyatta National Hospital. Do you have any questions/clarifications? I would be happy to answer the questions or clarify any concerns. Would you be willing to participate in the study and answer some questions on phone? ( ) Yes ( ) No Thank you for your time

KISWAHILI VERSION:

IDHINI YA KUPIGA SIMU
Muoneano wakliniki-patholojia, matibabu namatokeo ya matibabu ya wagonjwa walio na uvimbe msingi wa ovary aina ya sex cord-stromal tumours waliotibiwa katika hospitali ya kitaifa ya Kenyatta kuanziamwaka 2010 hadi 2020.
Mimi ni Daktari Walter Konya, mtafiti mkuu katika utafiti unaoangalia muonekao wa kliniki-patholojia, matibabuna matokeo ya matibabu ya wagonjwa walio na uvimbe msingi wa ovary waliotibiwa katika hospitali ya kitaifa ya Kenyatta. Utafiti huu utatathmini wagonjwa 96 waliotibiwa kuanzia mwaka 2010 hadi 2020, na wewe ni mmoja wao. Namba yako ya simu imeorodheshwa katika faili ya hospitali. Ninapiga simu kwa sababu ninahitaji msaada wako kufafanua baadhi ya habari ambazo hazipo au hazijulikani kutoka kwenye faili yako. Habari hizi zitatusaidie kukamilisha utafiti na kuelewa jinsi ya kudhibiti wagonjwa walio na uvimbe wa ovari aina ya sex cord-stromal tumour. Utafiti huu umeidhinishwa na hospitali ya kitaifa ya Kenyatta / Chuo kikuu cha utafiti na maadili cha Nairobi. Kamati ya Maadili imetoa idhini nitumie faili yako. Hakuna taarifa yako yoyote ya kutambua itakusanywa. Taarifa zilizokusanywa zitatumika tu kwa madhumuni ya utafiti huu. Maelezo yako yatawekwa siri. Simu itadumu kwa dakika tano. Tafadhali kumbuka kwamba simu inaweza kurekodiwa kwa madhumuni ya marejeleo. Ukichagua kutotoa habari yoyote au kuacha kutoa habari wakati wowote, haitaathiri matibabu itakayotolewa kwako au mpendwa wako katika hospitali ya kitaifa ya Kenyatta. Una maswali yoyote / ufafanuzi? Ningefurahi kujibu maswali au kufafanua wasiwasi wowote. Je, utakuwa tayari kushiriki katika utafiti na kujibu baadhi ya maswali kwenye simu? ( ) Ndiyo ( ) Hapana Asante kwa muda wako

APPENDIX 6 : ANTI-PLAGIARISM REPORT

Review of Clinico-Pathological Presentation, Management And Outcomes Of Patients With Sex Cord Tumours Of The Ovary Managed At KNH From 2012 To 2019.

by Dr Konya Walter P.

Submission date: 06-Oct-2020 04:23PM (UTC+0300)
Submission ID: 1406964843
File name: Dr_Konya_Walter_P.doc (224.5K)
Word count: 5439
Character count: 28726

Review of Clinico-Pathological Presentation, Management And Outcomes Of Patients With Sex Cord Tumours Of The Ovary Managed At KNH From 2012 To 2019.

ORIGINALITY REPORT

11%	6%	9%	3%
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