GRANULOSA CELL TUMOUR OF THE OVARY: A DESCRIPTIVE COHORT STUDY IN KENYATTA NATIONAL HOSPITAL.

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2023

DECLARATION

This dissertation is my original work and has not been presented for a degree in any other University.

Signature:  **Date**: 6th June 2023

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SUPERVISORS' APPROVAL

This dissertation has been submitted for examination with our approval as university supervisors.

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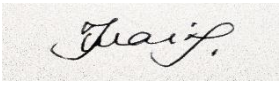
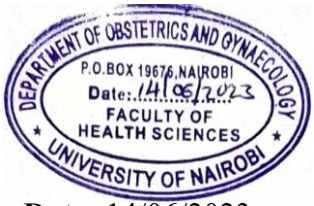
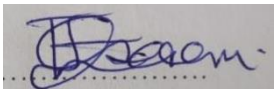
Signature:  **Date: 13th June 2023**

CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of **Dr. Ken Muthuuri Mworia** (Registration number H58/10856/2018) a master's student in the Obstetrics and gynaecology department, College of Health Sciences, The university of Nairobi, under the guidance and supervision of **Professor Zahida Qureshi** and **Dr. Musalia.** It has not been presented in any other university for award of a degree.



Signature:  **Date:** 14/06/2023

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DEDICATION

I dedicate my work to my family and friends. I am grateful to my loving parents, Isaiah Mworia, Rose Mworia, Raphael Thuranira & Nancy Thuranira whose words of encouragement have helped me achieve my goals. Special thanks to my siblings Dennis Kiogora, Maggie Kiogora and Jeff Mworia who have supported me through this process. Finally, I dedicate this work and give special thanks to my loving wife Imelda Kawira Muthuuri and son Neo Mutuma Muthuuri who inspire me each day to make the world a better place.

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Contents

LIST OF ABBREVIATIONS AND ACRONYMS

AGCT- Adult-type granulosa cell tumour

AMH - Anti-mullerian hormone

BEP – Bleomycin / etoposide / cisplatin

BSO - Bilateral Salpingo- Oophorectomy

FOXL2 – Forkhead box L2

GCT- Granulosa cell tumour

JGCT – Juvenile-type granulosa cell tumour

KNH – Kenyatta National Hospital

USO - Unilateral Salpingo- Oophorectomy

OPERATIONAL DEFINITIONS

Neoplasm of uncertain or unknown behaviour of the ovary – shall refer to a neoplasm of the ovary in the records department that's has not yet been classified.

Pre-menopausal – refers to patients who still have periods (whether regular or irregular) and are considered to be in their reproductive years or age < 50 years.

Post-menopausal – refers to the period of time after a woman has experienced 12 consecutive months without menstruation or age > 50 years.

Survival – refers to the length of time from the date of diagnosis that patients diagnosed with the disease are still alive.

Staging – refers to the categorization of the GCT based on the extent of the disease at the time of diagnosis.

GCT otherwise unspecified – refers to patients without a specific histological diagnosis of GCT that is neither AGCT or JGCT.

ABSTRACT

Background: Granulosa cell tumour (GCT) of the ovary is a rare neoplasm accounting for about 2% - 5% of primary ovarian neoplasms. The major functions of granulosa cells include the synthesis of sex steroids and various peptides required for folliculogenesis and ovulation. GCTs are a relatively homogenous group of tumors, categorised into two clear-cut subtypes, Juvenile GCT and Adult GCT. As stated by the World cancer report of 2020, there were approximately 12,000 cases of GCT worldwide. Although lower incidences of GCT are reported in Asian and African countries compared to Europe and North America, this has been partly attributed to under surveillance. In Kenya, there is lack of data on the characteristics of patients diagnosed with GCT.

Research objective: The broad objective was to evaluate the clinical characteristics, histological features and survival of patients managed for GCT of the ovary in KNH.

Study setting: The study took place in KNH - Health Information/ Records department as the patient's records were reviewed retrospectively.

Study design: This was a descriptive retrospective cohort study.

Sample size: A total of 44 patients' records with a histological diagnosis of GCT were reviewed.

Methodology: Patients records of women with histologically confirmed GCT of the ovary, managed in KNH from 2020 retrospectively were retrieved until the sample size was achieved or unless any logistical issues were encountered. Data was collected using a pre-developed and appraised data abstraction form. Phone calls were used to determine the patient's well-being and to acquire any critical missing data.

Results: The mean age of patients with a diagnosis of GCT from this study was 49.3 (SD 19.6) years, while the overall median age was 52.5 (IQR 33.5 – 61.5) years. The median age for AGCT (n=21) was 54.0 (IQR 42.0 – 63.0) while that for JGCT (n=5) was 17 (IQR 16.0 – 22.0) years. The youngest patient observed was 7yrs, while the oldest was 81yrs. The most common presenting symptom was abdominal pain & abdominal swelling. The most common symptom among those above 50yrs was post-menopausal bleeding. The most common sign was a palpable pelvic mass. Stage 1 disease was the most common stage at diagnosis. The most common histological subtype was AGCT with over 40% registered as GCT otherwise

unspecified on histology. The estimated overall survival rate was 91% at 2-years & 81% at 5-years. Patients with early-stage disease (stage I and II) had a very good prognosis at 100% while patients with advanced stage disease (stage III & IV) had a poor prognosis with an overall survival at 25%.

Conclusion: Despite the small number of patients in this study, we concluded that the majority of patients with GCT presented with abdominal pain, abdominal swelling and post-menopausal bleeding. The most common histological subtype was AGCT. Finally, we came to the conclusion that the survival of GCT patients managed in KNH is generally favourable due to presentation with early-stage disease while the few patients observed with poorer survival were noted to have presented with advanced stage disease.

Recommendations:

1. Further research into GCT possibly looking into prospective, randomised, well-controlled, multi-centre studies to look into post-operative adjuvant therapy for patients with advanced stage disease due to their poor prognosis in this study.
2. Improve record keeping and documentation of clinical features in the health records department to help follow up patients for longer periods of time due to the indolent nature of the disease & to gain more accurate information into their survival.

CHAPTER 1: INTRODUCTION

Granulosa cell tumours (GCT) account for 70% of sex cord-stromal tumours of the ovary & approximately 2% - 5% of all ovarian neoplasms(1–3). Granulosa cells are the somatic cells of the ovary which are closely connected with the developing oocyte. The major functions of granulosa cells include the synthesis of sex steroids & various peptides required for folliculogenesis & ovulation. GCTs are a relatively homogeneous group of tumours, categorized into two clear-cut subtypes, juvenile GCT (JGCT) & adult GCT (AGCT)(2,4).

Adult Granulosa cell tumor

The adult subtype (AGCT) composes 95% of GCTs and can occur at any age but usually presents during the peri-menopausal or early post-menopausal period, with a median age of diagnosis between 50 and 54 years in most studies (5). Women may present with proliferative breast disease, vaginal bleeding, irregular menstruation or amenorrhoea, infertility, post-menopausal bleeding etc. There is an established association between GCTs and endometrial neoplasms; 25-50% of patients have endometrial hyperplasia/intraepithelial neoplasia, whereas 5% of patients present with concurrent endometrial carcinoma(6–8). GCT is predominantly a sporadic tumour & not an exposure related cancer(9). In over 97% of cases AGCT are molecularly identified by a pathognomic somatic missense point mutation in transcription factor FOXL2 (Forkhead box L2)(1,10–12). FOXL2 is thought to play an important role as a tumour suppressor. Both types are almost always unilateral & can vary from microscopic foci to large, solid & cystic encapsulated masses. Tumours that are hormonally active have a yellow tint to their cut surfaces, due to intracellular lipids. Granulosa cells are organised microscopically in to a variety of different patterns including micro & macrofollicular, trabecular, bands & diffuse sheets. Call-Exner bodies (a characteristic rosette-like structure consisting of a central rounded pink mass that contains eosinophilic fluid encircled by a row of grooved or coffee bean nuclei) are commonly seen in the microfollicular pattern(4). Initial stage seems to be the single most critical prognostic factor associated with disease free survival in AGCT (13,14).

Juvenile Granulosa cell tumor

JGCT constitutes a small percentage, approximately 5% of this tumour type & commonly occurs in pre-pubertal girls & young women around 30 years of age(15). Most patients with JGCT present with isosexual pseudoprecosity, while others present with abdominal pain or swelling(15). Histologically, JGCT differ from AGCT in that uniform microfollicles i.e Call-

Exner bodies are rare and that mutations of the FOXL2 gene are seen rarely roughly in only about 10% of cases – This has led to some researches hypothesizing that the absence of this mutation in JGCT shows that it may be an entirely different tumor. JGCT has a good overall prognosis similar to AGCT, with only a 1.5% mortality associated with stage Ia tumors, however the outlook is more guarded in patients with stage Iaii or stage Ic tumors and poor in those with stage II tumors.

The two main characteristics that differentiate GCT of the ovary from other ovarian neoplasms, is that GCT's can lead to irregularly secreted hormones e.g. estrogen, inhibin & Anti-Mullerian hormone (AMH) & that they behave like low-grade malignancies with good prognosis(6,16). Of note, sometimes GCT can produce androgens, causing virilizing symptoms and hirsutism(17).

In both subtypes, early & complete surgical resection remains the leading evidence based treatment(18). For most patients, unilateral salpingo- oophorectomy (USO) with preservation of the contralateral ovary & the uterus was found to be suitable in early stage disease if endometrial hyperplasia and endometrial carcinoma have been excluded through endometrial sampling (12,19). For patients with more than Stage 1A, surgery should include total abdominal hysterectomy (TAH) & bilateral salpingo-oophorectomy (BSO)(4,12,20). Postoperative adjuvant chemotherapy is ideal for patients with resected high-risk AGCT(12,21). The usefulness of radiation treatment in GTC is not clear-cut but in well debulked cases radiation after surgery is an applicable option(12). Due to the uncertain risk of recurrence in AGCT even after years of clinical cure of the prime tumour, long-term follow-up with clinical inspection & serum tumour markers e.g. Inhibin B, estradiol or AMH is ideal(22–24). It is important to note that testosterone and its precursors can be used as markers for tumour progress in GCTs that secrete androgens.(17,25). About 10-30% of GCT recur after 4-7 years after the primary surgery of which about 55% have consecutive recurrences(10,23). Multiple site recurrences are common and nearly half are asymptomatic(23).

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology

As maintained by the World Cancer Report of 2020, there were about 295,414 new instances of ovarian cancer around the globe in 2018 and therefore, approximately 12,000 cases of AGCT. The global incidence of GCT is unknown. Despite the lack of a global incidence for GCT what we do know from previous studies such as one done by Bryk et al. in 2017 covering four Scandinavian countries (Finland, Norway, Iceland and Sweden over a 60 year period) is an age-adjusted incident rate of 0.6 - 0.8 per 100,000 for most of the study period. (9)Other studies such as one done in Netherlands, Sweden, Israel, Denmark and Finland showed an incidence rate of 0.5 – 1.4 per 100,000 while in the US they had an occurrence rate of about 0.99 per 100,000 women.

The same study by Bryk et al. in 2017 showed an age-standardized rate which was the most between fifty and sixty-four years. There were no jobs with statistically significantly increased risk of GCT. During the sixty-year period analysed between 1953 – 2012, big changes in the use of contraceptives, post-menopausal hormone therapy, fertility rate and lifestyle did not appear to have a significant outcome on the incidence of GCT.

The studies done on race and ethnicity as concerns the epidemiology of AGCT are contradictory(9,26). Women of European/American descent were twice as likely as women of Asian/African origin to develop AGCT according to Ohel et al. Boyce et al. on the other hand described significantly more blacks, Asians and Hispanics among AGCT patients in a case-control study comparing AGCT patients with the community & with patients with epithelial ovarian tumours. Research based on The United States Surveillance, Epidemiology & End Result program (SEER) came to the conclusion that white women, similar to findings by Ohel et al. had higher rates of epithelial tumours than women of African descent, whereas the contrary was correct for sex cord-stromal tumours.

In Africa, however, the incidence rate is relatively lower than in high income countries. Epidemiological studies in Kenya have focused on more common cancer types such as epithelial ovarian cancers, cervical & breast cancer, with minimal mention or identification of GCT.

2.2 Clinical presentation

Symptoms and diagnosis

In GCT classical symptoms include menstrual disturbances and post-menopausal bleeding (due to estrogen secretion) as well as bloating and abdominal pain (due to mechanical distension)(2,6,7,11,12). The high blood supply of AGCTs may in some cases lead to tumour rupture, with intra-abdominal haemorrhage & sudden lower abdominal pain(27). Endometrial hyperplasia or carcinoma may be induced from estrogen, derived from hormonally active tumours as shown by Schumer et al(28). Ayhan et al. however noted that AGCT may present without any clinical symptoms and discovered in a routine hospital visit.

A unilateral ovarian mass in an old woman accompanied with menstrual disturbances, post-menopausal bleeding or endometrial abnormalities should raise a suspicion of GCT. How AGCT looks on ultrasound can vary anywhere from cystic to solid although the most common presentation is a solid & cystic mass with periodic bloody fluid.

GCTs are characterised by inhibin secretion, and this tumour marker can be used for monitoring tumour progression and response to therapy. These tumours also frequently produce estrogen, but estrogen is not a good marker because it is not specific to GCTs (2,6,10,12,30). Studies have found that serum AMH is a sensitive, specific, and reliable marker of the AGCTs. Of significant importance, serum AMH was found to be sensitive and specific for early detection of recurrence of GCT after having undergone oophorectomy (31). Because AGCTs have high incidences of recurrences even 10-20 years after resection, this finding is of prime importance for this condition(32).

2.3 Staging

The sole clinical prognostic factor that is of note in almost every study is the stage of tumour(13,33,34). Tumour recurrence, overall survival and disease-related survival are associated with stage of disease(13,27,33,35). The five-year survival rates reported in literature are encouraging and range from 75% - 95% in stage 1 disease and 55% - 75% in stage II & 22% - 50% in stage III and IV tumours(36).

2.4 Treatment

According to Seagle et al. in 2017 early and complete surgical resection remains the best evidenced treatment for ovarian GCT. In a study conducted by Gershenson et al. in 1994, it was shown that laparotomy was initially indicated for both diagnosis and treatment for young women suspected of having GCT. For a majority of patients, unilateral salpingo-oophorectomy (USO) with preservation of the contralateral ovary and the uterus was found to be appropriate in early-stage disease. The basis for this surgical approach has been based on several studies, one of note being done by Piura et al. in which the researcher showed an equivalent cure rate for patients who underwent unilateral or bilateral adnexectomy for early-stage IA disease. However, it is necessary to note that in addition to USO, dilatation and curettage was done in such patients to rule out endometrial precancerous and cancerous changes before concluding on the mode of treatment. To add onto that, a study done by Wang et al. reported a pregnancy rate of 86% and a live birth rate of 95% among patients who underwent fertility sparing surgery; demonstrating USO to be a viable treatment option for early stage disease(37). Radical surgery for such patients can be postponed until recurrence, provided they are willing to undergo a prolonged follow up. Surgical route does not affect the oncological safety of patients with stage 1 AGTCs, with comparable outcomes between laparoscopic and open approaches(38). In early-stage disease, standard pelvic and/or para-aortic lymphadenectomy is not mandatory due to the very limited rates of involvement of the lymph nodes in primary AGCT, as shown by Cheng et al in 2018(27,37,39–41). For patients with more than Stage 1A, surgery should include TAH and BSO(12,20).

2.5 Adjuvant treatment

Postoperative adjuvant chemotherapy is recommended for patients with resected high-risk AGCT above stage 1A(12). The current recommended regimen for GCT is optimal debulking followed by 4 cycles of bleomycin, etoposide and cisplatin (BEP) a combination that appears to result in at least a 95% cure rate for stage 1 disease and at least a 75% cure rate for advanced stage disease(40,42). A study done in 2018 by Oseledchyk et al. involving a total of 739 patients with surgically treated AGCT, notably showed that administration of adjuvant chemotherapy was not associated with improved five-year disease specific survival regardless of stage similar to several earlier studies conducted by Uygun et al. in 2003, Lee et al. in

2011, Kottarathil et al. in 2013, Meisel et al. in 2015, Mangili et al. in 2016 and Seagle et al. in 2017(43–46). Despite the debate about the benefit of adjuvant therapy, the policy in most hospitals is to give postoperative adjuvant combination chemotherapy to patients in whom apparent spread of the GCT beyond the ovaries has occurred.

The effectiveness of radiation in the treatment of GCT is not clear but in selected patients postoperative radiation therapy is a viable option(5). A study done by Savage et al. showed that for patients with inoperable disease radiotherapy produced a number of long-term remissions with an overall response rate of 50%.

2.6 Follow - up

For a typical AGCT patient, follow up entails regular hospital visits with gynaecological exams, a pelvic ultrasound & serum tumour markers(9). As shown by Farkkila et al. inhibin B and AMH are the most sensitive and specific tumour markers. In the backdrop of recurrence, tumor markers are usually increased and correspond well with burden of disease. The current European Society for Medical Oncology (ESMO) recommendations of 2018 advise for the period of routine clinical follow up to be in 3 monthly intervals for the first three years, followed by 6 monthly intervals from the beginning of the third year and that this frequency should be maintained indefinitely due to the indolent course of the disease with tendency for late recurrence. For patients who have undergone fertility sparing surgery, such as a USO in early-stage disease, a pelvic ultrasound should be carried out every 6 months. A CT scan or MRI should be carried out when indicated and based on symptoms & tumour marker elevation in order to assess the presence of tumour outside of the pelvis or in multiple sites around the body.

2.7 Recurrence

GCT have a reputation for a comparatively good prognosis and proclivity for late relapse(14). The rate of tumour recurrence, in recent times has been wide ranging from five percent to sixty four percent with the median time to relapse between three and a half to twelve years. When compared with epithelial ovarian tumours, GCT have demonstratively better survival rates due to their indolent nature. The common locations for tumour recurrence often include the intra-abdominal cavity and the pelvis, but it is not uncommon to be seen in the bone, lung, retroperitoneal space, liver, pelvic or para-aortic lymph nodes(47). In up to 50% of patients

with relapse it has been observed that they may present with multiple sites of recurrence(23). In cases of advanced disease, adjuvant treatment is necessary, while in confined recurrences, surgical debulking is the therapy of choice. Due to the high mortality rate (over 70% in some series) in patients with recurrent tumours, it is important to emphasize the importance of prognostic tools in finding those at an increased risk of relapse (48).

2.8 Survival

With GCT most patients present with early stage disease and thus survival is generally excellent(36). According to a study by Uygun et al in 2003, there were only two significant factors for overall survival after univariate analysis- stage and presence of residual disease. Stage of disease has been the only factor shown consistently to affect survival of patients(12). The 5-year overall survival rate for GCT in literature varies from 84.6% - 91% shown by Khosla et al in 2014 and Ayhan et al in 2009 to as high as 99% - 100% by Bergamini et al in 2018 and Lauszus et al in 2001. Patients with early-stage disease such as those in stage I & II have an excellent prognosis with 5-years overall survival approaching 94% - 99% and usually the patients do not require any post-operative treatment. In advanced stage disease (stage III & IV) the 5-year overall survival is between 33% - 80% and thus the choice of post-operative therapy with 4-cycles of BEP should be examined in such patients(12,49). The mean overall survival in literature ranges from 9 years by a study done by Malmstrom et al in 1994, 12 years in a study by done by Ayhan et al in 2009 and 13 years in a study by Dridi et al in 2018 (Tunisia).

2.9 Prognostic factors

Several studies have proposed to look into the clinical prognostic factors for AGCT. (13,35,50–52). Out of all of the studies done, only tumor stage emerged as the clinical prognostic factor that was reported definitely in almost all of the research(9). In a recent study done by Karalok et al. in 2016 a correlation was made between poorly differentiated tumors with return of disease, but not with disease-related mortality(53). In four studies concluded recently, the presence of left over tumor after initial therapy was connected with AGCT recurrence in multi-level analysis, calling to attention the need for complete tumor reduction at the beginning of treatment (18,21,38,54). Poor prognostic factors such as inadequate surgical staging and management outside a referral centre were shown by Mangili et al. in 2013 to affect recurrence, but not disease-specific survival.

JUSTIFICATION

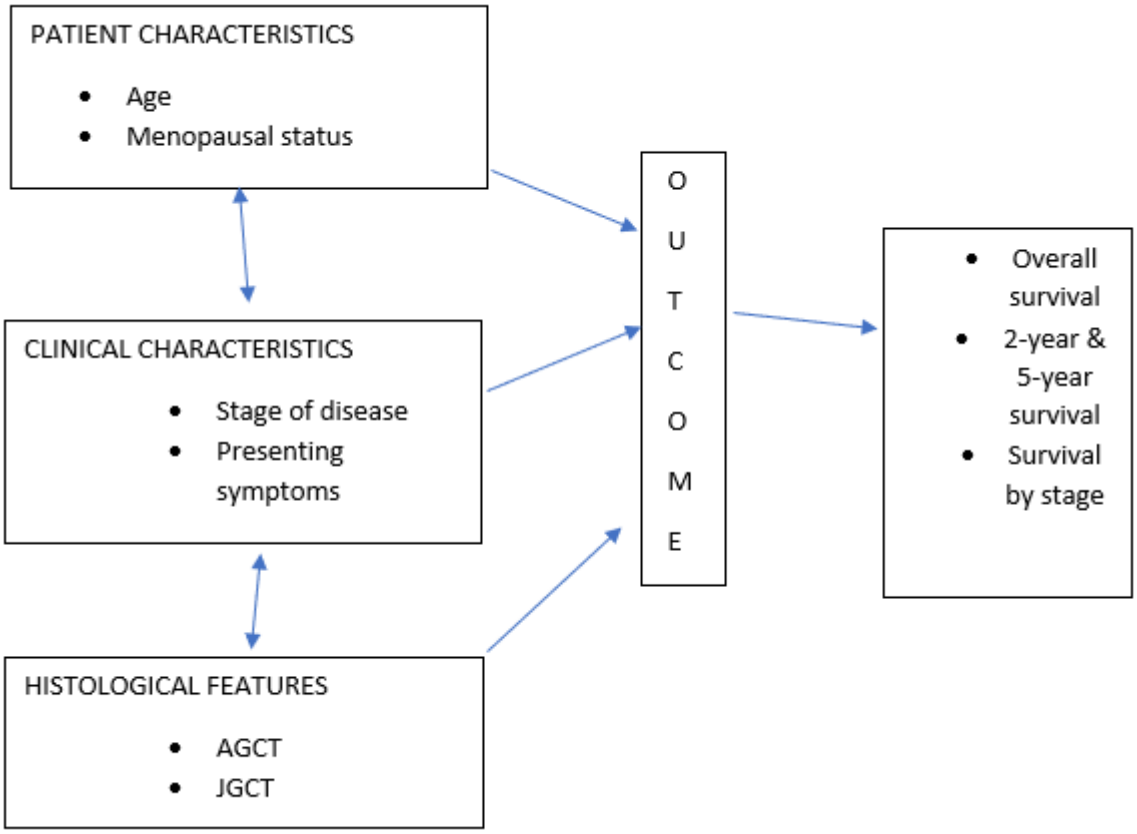
Globally, cancer causes more deaths than Tuberculosis, Human Immunodeficiency Virus (HIV) and Malaria combined(55). In Kenya, cancer is now the 3rd leading cause of deaths and 2nd among non-communicable diseases accounting for 7% of overall mortality rate. According to the World Cancer Report (2020) there were about 295,414 new cases of ovarian cancer worldwide in 2018 and thus, the estimated annual number of AGCTs was approximately 12,000. Ovarian cancer is the third commonest cause of cancer death from gynaecologic tumours in Kenya and the fifth cause of cancer related death in women worldwide(55,56).

There is insufficient information on GCT in Africa and in Kenya to be precise. There is paucity of information on the socio-demographic, clinical characteristics, histological features and survival of patients managed for GCT. Lack of locally available data may compromise the possibility of establishing an evidence-based practice that is locally engendered.

The study is necessary at this point in time to help in delivering quality care, setting preventive strategies and understanding the nature of the disease from locally informed data. The data collected will also play a crucial role towards defining the condition in Kenyan context based on the demographic characteristics of patients diagnosed with GCT. In the end, the study will contribute towards building the body of literature and make it possible to compare disease characteristics and survival between Kenya and other countries. Ultimately, the findings from this study may come in handy in policy formulation as regards GCT or eliciting a chain of future studies on the condition that can result in better understanding and improvement of care models.

2.10 CONCEPTUAL FRAMEWORK

Figure 1: Diagrammatic representation of conceptual framework



Conceptual framework narrative

The conceptual framework illustrates the interaction between the major variables involved in this study. There are four broad components highlighted in the framework, which include patient characteristics, clinical characteristics, histological features and their outcomes. Factors such as age & menopausal status have significant influence on management, clinical presentation & survival. For example, a patients age & stage of disease have been assessed as prognostic factors in a number of retrospective cohort studies(9). The outcomes, which in this case shall look at the overall survival, 2-year & 5-year survival rates and survival by stage is influenced by demographic factors and the clinical-pathological characteristics such as initial stage of disease. Therefore, all four major categories (patient characteristics, clinical characteristics, histological features and outcomes) are interlinked; thus, the conceptual framework is best suited to create a pictorial illustration of the influence each of the categories has on the other as illustrated above in **Figure 1**.

2.11 RESEARCH QUESTION

What are the clinical characteristics, histological features and survival in patients managed for Granulosa cell tumour of the ovary in KNH?

2.12 OBJECTIVES

2.12.1 Broad objective

To evaluate the clinical characteristics, histological features & survival in patients managed for Granulosa cell tumour of the ovary in KNH.

2.12.2 Specific objectives

Among patients managed for Granulosa cell tumour of the ovary in KNH: -

1. To determine the clinical characteristics
2. To ascertain the histological features
3. To evaluate the survival of patients (2-year and 5-year)

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN:

This was a descriptive retrospective cohort study. In this study, patient's files of women who had a histologically confirmed diagnosis of Granulosa cell tumour of the ovary managed in Kenyatta National Hospital were reviewed from 2020 retrospectively until the sample size was achieved or unless any logistical issues were encountered. The outcome of interest was survival which included overall survival, 2-year & 5-year survival rate and survival by stage of the disease.

STUDY AREA: Health Information/ Records department in KNH.

3.2 SPECIFIC STUDY SITE AND SETTING:

The study was conducted in Kenyatta National Hospital (KNH) which is located in Nairobi City County, the capital city of Kenya. KNH is the biggest referral hospital in the country and within the East and Central Africa.

KNH has several speciality departments, among the obstetrics and gynaecology department, under which gynaecological unit (the gynae-oncology ward and the outpatient gynaecology clinic) operates. Gynaecology oncology departments serve roughly 1,100 cases annually. The hospital has laboratory technology to undertake histologic diagnosis and has gynae-oncologists who manage cases of GCT. KNH handles cases referred from different parts of the country, and is the gynae-oncology centre of choice for those seeking health care services in public hospitals. It therefore provided a suitable representation of the demographic characteristics of GCT patients in Kenya. The records of these women were retrieved by the health records department where the data collection happened.

Patients diagnosed with GCT in KNH are managed based on specific patient characteristics. However, the standard management offered is USO for stage 1A with no adjuvant chemotherapy and TAH/BSO with 4 cycles of BEP for stage 1B and above. Patients are then followed up in the Friday oncology clinic periodically.

3.3 STUDY POPULATION:

The study population was women with histologically confirmed GCT of the ovary, managed at KNH from 2020 retrospectively until the sample size was achieved or unless any logistical challenges were encountered. Histological diagnosis was essential in this case to ascertain the cancer diagnosis and, therefore avoid inclusion of misdiagnosed cases. Only women whose condition was managed at KNH was included because the study relied on patients' health

records. Those with other reproductive cancers were excluded because it would be difficult to disaggregate the effect of GCT on outcome from that of other cancers for example concomitant GCT and endometrial cancer.

3.3.1 INCLUSION CRITERIA:

The inclusion criteria included women with a histologically confirmed diagnosis of Granulosa cell tumour of the ovary, managed in KNH.

3.3.2 EXCLUSION CRITERIA:

1. Patients with another co-existing malignancy
2. Incomplete records missing critical data for example a missing Histology report or missing more than 50% of information from the data abstraction form.

3.4 SAMPLE SIZE JUSTIFICATION:

Using the Fischer's formulae, the sample size was calculated as follows: -

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

Where:

n = Sample size

Z = Normal deviation at the desired confidence interval. In this case it will be taken at 95%, Z value at 95% is 1.96

P = The proportion of the population with the desired characteristics from a study by Kottarathil et al. in 2013 "Recent advances in Granulosa Cell Tumour Ovary: A Review" is approximately 5%

d^2 = Degree of precision, will be taken to be 5%

$$n = \frac{1.96^2 \text{ X } 0.05 (1-0.05)}{0.05 \text{ X } 0.05}$$

$$n = \frac{3.8416 \text{ X } 0.05 (0.95)}{0.0025}$$

$$n = \frac{0.182476}{0.0025}$$

n = **73**

3.5 SAMPLE PROCEDURE

All eligible files of patients with the diagnosis of neoplasm of the ovary and neoplasm of uncertain or unknown behaviour of the ovary were identified from the records department from 2020 retrospectively until the sample size was achieved or unless any logistical issues were encountered. All patients' files with histologically confirmed GCT of the ovary were extracted that fulfilled the inclusion criteria.

3.6 DATA COLLECTION AND MANAGEMENT

The data was collected using a pre-developed and appraised data abstraction form. (**See appendix B**). The tool was pre-tested before commencing the actual data collection to ensure that the tool was feasible, valid and reliable. The study tool contained sections for demographic data, clinical characteristics, histological features and survival. The principal investigator and 2 research assistants identified the appropriate patients' files from the KNH Health records department registry with a diagnosis of neoplasm of the ovary or neoplasm of unknown origin and only files that fit the inclusion criteria with a histological diagnosis of GCT of the ovary were isolated. Using the data abstraction form as a guide, the relevant data was abstracted from each file. Each patient's data was then entered into a respective copy of the study tool with a unique study number. Data was abstracted from all available medical records including doctors' notes, laboratory and diagnostic reports, referral letters and all other relevant reports in the files. The forms were checked for completeness by the research assistants. Telephone numbers of participants and their next of kin were obtained from the files and were contacted by phone to ascertain their well-being and to inquire on any missing data. The purpose and process of the study was explained to those contacted by phone and consent sought. A telephone interview was done if the patient or next of kin was willing to participate.

The phone calls were only used to determine the patient's well-being & to acquire missing data. The research assistants notified the principal investigator of any critical data missing from the files and assisted in making a follow-up using the phone contacts provided in the patients' file. The principal investigator introduced himself and highlighted the study topic and objectives before obtaining a verbal consent over the phone using the verbal consent

form (**Appendix A**). The patient was notified that they were at liberty to choose not to provide the data requested and if they accepted was documented in the data abstraction form. After data collection the questionnaires were placed in a locked cabinet for purpose of confidentiality. Filled questionnaires were given to the statistician who entered data in an excel spread sheet and analysis done with Statistical Package for social sciences (SPSS) version 22 software. For my **first objective,** demographic and clinical characteristics were analysed and presented as frequencies and proportions for categorical data, and as means with standard deviation or medians with interquartile range for continuous data. For the **second objective,** the histological features were analysed and presented as frequencies and proportions. The **third objective** to evaluate survival was analysed with the use of Kaplan Meier method. Hazards ratio with 95% confidence interval were calculated where applicable. All statistical analysis was considered significant where the p-value < 0.05.

3.7 ETHICAL CONSIDERATIONS

Ethics approval to carry out the study was sought from the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UON ERC) before collection of data. Permission was also sought from Kenyatta National Hospital administration to be allowed to access patients' files from the Health records department and extract relevant data. The purpose of the study was explained to participants contacted by phone and verbal consent sought. Patient's privacy and confidentiality was upheld by ensuring the data collection tool contained no identifying information. No patient's identification details were used during data analysis as study numbers were used in entering data. The study did not pose any risk to the patient care given that it was evaluating already documented care as opposed to introducing or evaluating care prospectively.

3.8 LIMITATIONS

Limitations encountered involved the small sample size due to the rarity of the tumour, the retrospective nature of the study which relied mainly on secondary data which was subject to poor record keeping & missing files. Other limitations encountered included using phone calls as a complimentary data collection approach as some informants declined to share their details as requested, some calls went unanswered, while other informants queried the legitimacy of the process and complained of breach of their privacy.

CHAPTER 4: RESULTS

A total of 44 patients records files who fit the eligibility criteria were reviewed.

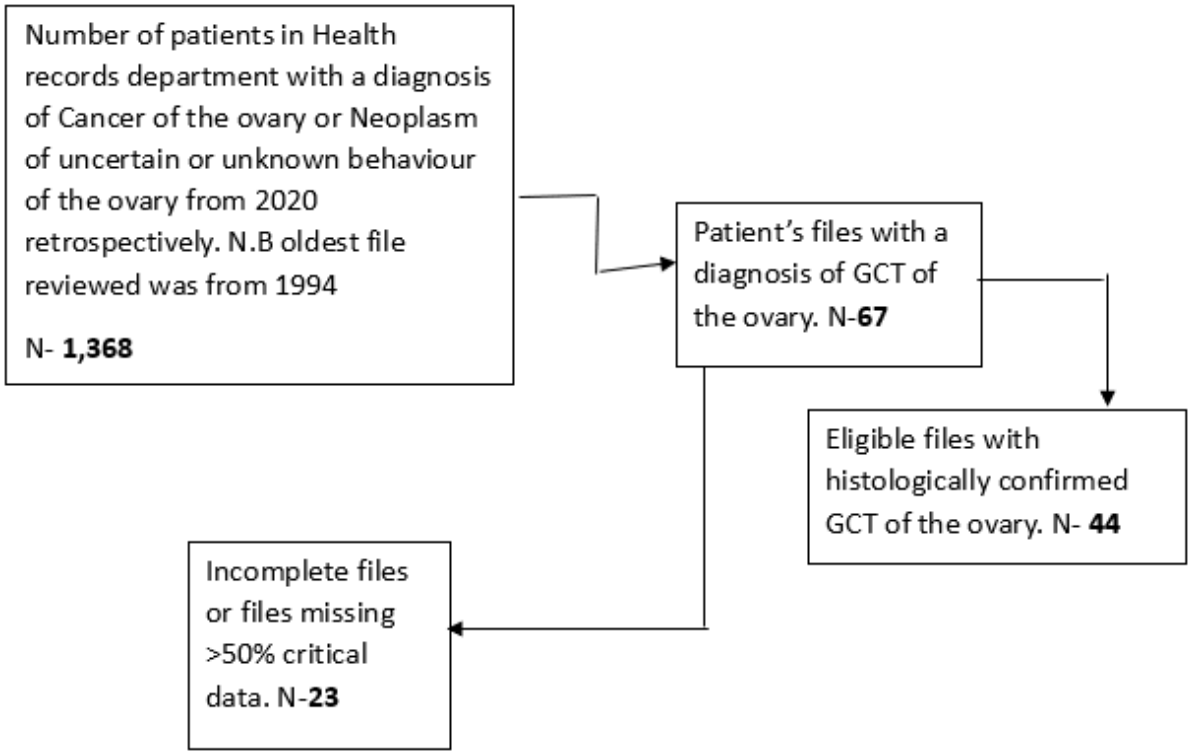


Fig 2. Schematic representation of study flow chart

A total of 44 patients records files who fit the eligibility criteria were reviewed. Results were presented in tables.

Table 1: Patient characteristics

		Frequency (n-44)	**Percentage (%)**
Age (years)	<18	3	6.8
	18-35	9	20.5
	36-55	17	38.6
	56-75	11	25
	>75	4	9.1
Marital status	Single	19	43.2
	Married	25	56.8
Education	Primary	11	25
	Secondary	13	29.5
	Tertiary	9	20.5
	Missing	11	25
Employment status	Employed	15	34.1
	Unemployed	15	34.1
	Student	3	6.8
	Missing	11	25

Table 1 shows a total of 44 patients who participated in the study. The average age of the women in this study was 49.3 (SD of 19.6) years. 6.8% of the women were below 18 years of age, majority of the women were between 36 – 55 years of age (38.6%). Twenty-five (56.8%) were married while nineteen (43.2%) were single. Eleven patients (25%) had achieved a primary level of education, thirteen (29.5%) secondary and nine (20.5%) tertiary level of education. In terms of employment status there was an equal distribution between those employed and unemployed at 34.1%.

Table 2: Presenting symptoms

		Frequency	Percentage of patients (n=44)
Symptoms	Abdominal swelling	30	68.2%
	Abdominal pain	25	56.8%
	Post-menopausal bleeding	17	38.6%
	Amenorrhoea	6	13.6%
	Infertility	2	4.5%

Table 2 shows the symptoms patients being managed for GCT presented with to the hospital. Thirty patients (68.2%) presented with abdominal swelling, twenty-five patients (56.8%) presented with abdominal pain, seventeen patients (38.6%) presented with post-menopausal bleeding, six patients (13.6%) presented with amenorrhoea while two patients (4.5%) presented with infertility. The most common presenting symptoms across the board was abdominal pain and abdominal swelling, while the most common presenting symptom for patients above 50years old was post-menopausal bleeding.

Table 3: Clinical signs

		Frequency	Percentage of patients (n-44)
Sign	Ascites	10	22.7
	Anemia	4	9.1
	Palpable pelvic mass	35	79.5

Table 3 shows the clinical signs found on examination of patients with GCT of the ovary. The majority of patients (79.5%) were found to have a palpable pelvic mass on examination while ten patients (22.7%) had ascites and four patients (9.1%) were found to have anemia.

Table 4: Initial stage at diagnosis

		Frequency (n-44)	Percent (%)
Stage	1	18	40.9
	2	3	6.8
	3	3	6.8
	4	1	2.3
	Missing	19	43.2

Table 4 shows the initial stage at diagnosis of patients managed with GCT. The majority of patients (40.9%) presented in stage 1. Three patients (6.8%) presented in stage 2 and 3 respectively while one patient (2.3%) presented in stage 4.

Table 5: Menopausal status

		Frequency (n=44)	Percent (%)
Menopausal status	Pre-menopausal	18	40.9
	Post-menopausal	26	59.1

Table 5 shows the menopausal status of the patients managed for GCT. The majority of patients twenty-six (59.1%) were post-menopausal while eighteen (40.9%) on presentation to the hospital were pre-menopausal.

Table 6: Histological type

		Frequency (n=44)	Percent (%)
Histological type	AGCT	21	47.7
	JGCT	5	11.4
	GCT otherwise Unspecified	18	40.9

Table 6 shows the histological diagnosis of patients with GCT. Twenty-one patients (47.7%) were found to have a histological diagnosis of AGCT which was the most common, five patients (11.4%) had a histological diagnosis of JGCT while eighteen (40.9%) had a histological designation of GCT otherwise unspecified.

Table 7: Survival of patients at 2 years

	Frequency (n=44)	Percent (%)
Alive	30	68.2
Dead	3	6.8
Unknown	1	2.3
N/A	10	22.7

Table 7 shows the survival of patients at 2 years which was estimated at 91%. Of the thirty-four patients who were eligible to be assessed for survival, thirty patients i.e the vast majority, were alive at the end of the 2 years.

Table 8: Survival of patients at 5 years

	Frequency (n=44)	Percent (%)
Alive	13	29.5
Dead	3	6.8
Unknown	2	4.5
N/A	26	59

Table 8 shows the survival of patients at 5 years which was estimated at 81%. Of the eighteen patients who were eligible to be assessed for survival, thirteen patients were alive at the end of the 5 years.

Table 9: Survival by stage (2 year and 5 year)

		Patient distribution by stage (n=44)	Number of patients dead at 2 years	Number of patients dead at 5 years	Survival by stage	
Stage of disease at diagnosis	1	18	0	0	100%	
	2	3	0	0	100%	
	3	3	2	2	33%	
	4	1	1	1	0%	
	Missing	19				
Total dead				3		

Table 9 shows survival according to stage of disease. Patients with stage 1 and 2 disease had an excellent rate of survival at 100%. This dropped to 33 % for patients in stage 3 and a 0% rate of survival for patients in stage 4.

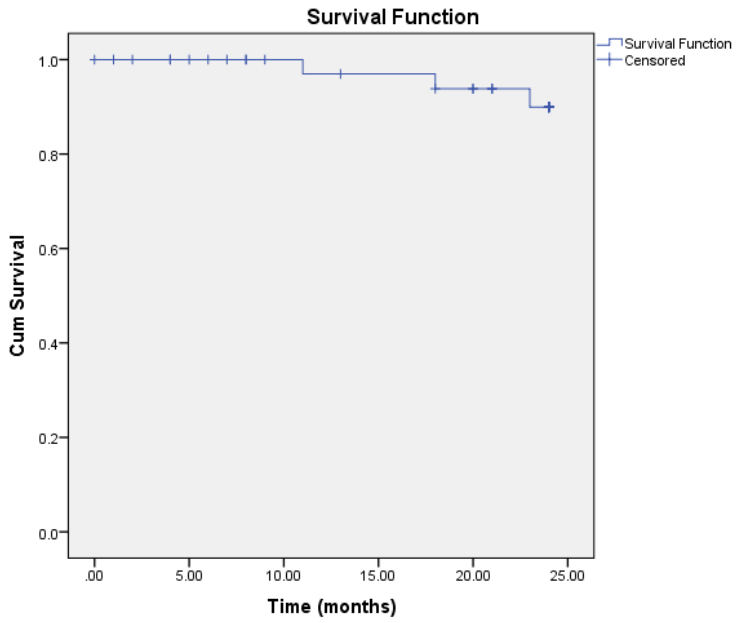


Fig 3: Kaplan-Meier Survival analysis curve

Figure 3 shows the Kaplan -Meier survival curve for 2 years showing patients with GCT of the ovary having a good prognosis.

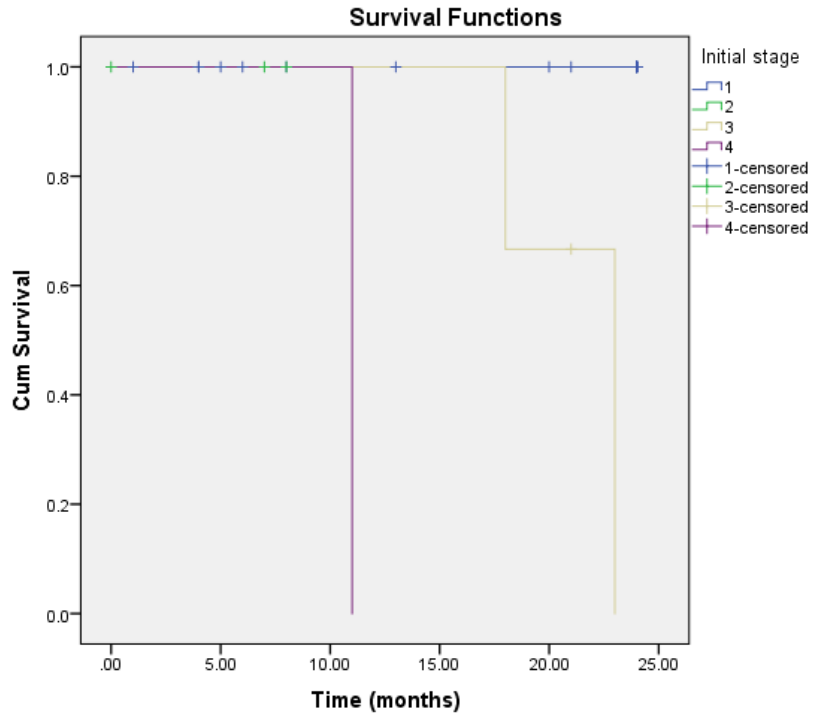


Fig 4: Kaplan-Meier survival curve by stage of disease

Figure 4 shows the Kaplan -Meier curve by stage of disease indicating good survival for stages I and II and poor survival for stages III and IV.

CHAPTER 5: DISCUSSION

Granulosa cell tumor of the ovary is a rare neoplasm, accounting for approximately 2-5% of ovarian neoplasms. In our study there were 1,368 patient's files reviewed with a diagnosis of ovarian carcinoma and 44 of them (3.2%) were GCT with a mean age of 49.3 (SD 19.6) years. The youngest age observed was 7 years old while the oldest was 81 years old. The overall median age was 52.5 (IQR 33.5 – 61.5) years. The median age for AGCT (n=21) was 54 (IQR 42.0 – 63.0) years while that for JGCT (n=5) was 17 (IQR 16.0 – 22.0) years. These results indicate that GCT is an uncommon gynaecologic malignancy. AGCT can occur at any age but usually presents during the perimenopausal or early postmenopausal period with a median age of diagnosis between 50 and 54 years, while JGCT commonly occurs in pre-pubertal girls and young women around 30 years of age in accordance with the literature.

The most common presenting symptom from our study was abdominal pain and abdominal swelling. In GCT classical symptoms include menstrual disturbances, postmenopausal bleeding, bloating and abdominal pain (2,6,7,11,12). This is due to GCT tumors usually being large and vascular causing pain by one, mechanical distension of nearby pelvic structures and two, occasionally rupturing resulting in abdominal pain, haemoperitoneum and hypotension mimicking an ectopic pregnancy. The most common presenting symptom among patients above 50 years from our study was post-menopausal bleeding. This is due to GCT elaborating large amounts of estrogen which can lead to endometrial hyperplasia in 25-50% of patients and even endometrial carcinoma in about 5% of women with such steroid producing tumors. The most common sign was a palpable pelvic mass on examination which was subsequently confirmed on ultrasonography and was similar to what was found in similar studies. Ayhan et al. however noted that AGCT may present without any clinical symptoms and may be discovered in a routine hospital visit.

From our study the majority of patients presented with early-stage disease, with the majority in stage 1. Early presentation to a healthcare facility with GCT of the ovary, unlike other epithelial tumors, is due to the production of large amounts of sex-steroids producing specific symptoms that alert patients to seek intervention such as abdominal pain, abdominal swelling, abnormal uterine bleeding, irregular menses, breast changes, amenorrhea, infertility, precocious puberty and in some cases virilizing effects due to the production of androgens. This leads to patients being examined, investigated and referred sooner to tertiary facilities for further work-up as compared with other ovarian neoplasms that usually have vague, non-

specific symptoms. From our study, patients presented to a tertiary health care facility on average within 14 months from start of symptoms, with post-menopausal patients who presented with bleeding presenting much earlier on average at about 8 months. Patients with vague symptoms such as infertility, amenorrhea, breast changes on average presented much later to a tertiary facility averaging about 30 months. This was due to several factors, such as low index of suspicion due to the unusual presentation and poor referral systems in primary health facilities.

The most common histological type from our study was AGCT. Granulosa cell tumors are broadly divided into adult and juvenile granulosa cell tumors, largely based on the age of the patient but also on morphologic findings. This was comparable to findings in other studies with AGCT accounting for 95% of cases and JGCT accounting for approximately 5%. Of note 40% of cases were labelled as GCT otherwise unspecified due to the morphological criteria and the fact that sometimes JGCT are undifferentiated which might lead them to not being put in any specific category.

In our study we found the estimated overall survival at 2-years was 91% and at 5-years was 81%. Our findings were comparable to those found in other studies where patients had a favourable overall survival rate due to early presentation to a health care facility, leading to early diagnosis and management unlike the poorer survival noted in patients with epithelial ovarian tumors who usually present late. As stated earlier, stage has been universally accepted as an important prognostic factor. Our study showed that the survival rates in stage 1 and 2 disease were 100% at 2 and 5 years respectively. However, patients with advanced stage disease i.e stage 3 and 4 in our study had an estimated combined overall survival of 25% which was low in comparison with other studies which still showed a favourable survival for patients with advanced disease at 80% like by Kottarathil et al. This is due to several factors such as initial management outside a tertiary facility without input from a gynae-oncologist, incomplete or wrong staging, incorrect surgery done for example USO in advanced disease instead of TAH/BSO, residual disease after surgery, patients missing post-operative adjuvant chemotherapy and poor follow up. Most patients were lost to follow up after initial surgery and after completing chemotherapy. Several factors contributed to this poor follow up. Several reasons included a majority of patients believing that after initial management i.e TAH/BSO + completing 4 cycles of BEP that they were cured, while others highlighted the high cost of follow up including transport to hospital, consultation fees, cost of imaging studies & tumor markers such as Inhibin B (averaging 8,000Ksh) and the lack of

tertiary facilities close to their county of origin. The most common tumor marker found in patients files was Cancer antigen-125 & estradiol. CA-125 was often ordered due to the initial suspicion of the ovarian neoplasm being of epithelial origin while estradiol was commonly ordered due to the investigation being readily available & affordable in the hospital. Few patients were followed up with Inhibin B or AMH as a tumor marker due to its prohibitive cost and lack of availability in the hospital only being found in specialized labs. Common factors among the patients who died (n=3) during the study period included late referral to a tertiary health care facility, incorrect surgery e.g USO being done for a patient with advanced stage disease instead of a TAH/BSO (which would have been appropriate), poor follow up and presence of residual disease after surgery.

5.1 CONCLUSION

Despite the small number of patients in this study, we concluded that:

1. Majority of GCT patients presented with abdominal pain, abdominal swelling and post-menopausal bleeding.
2. The most common histological subtype was Adult granulosa cell tumor of the ovary.
3. The survival of our GCT patients is generally favourable due to presentation with early-stage disease while the few patients observed with poorer survival were noted to have presented with advanced stage disease.

2.2 RECOMMENDATIONS

1. For postmenopausal patients with symptoms such as progressive abdominal pain, abdominal swelling and post-menopausal bleeding & pre-menopausal patients with unexplained infertility, amenorrhea, irregular menses and precocious puberty to seek health care early and prompt referral to a tertiary health care facility as early detection of GCT has a good survival.
2. For all patients to undergo correct & complete staging with documentation during surgery as early-stage disease is associated with good outcomes.
3. For improved pathology service, for patients to undergo full histological subtype analysis into either AGCT or JGCT in the pathology department with novel biomarkers instead of being labelled as GCT otherwise unspecified, as the subtypes behave as different entities and for intra-operative frozen section of pathological specimens to be made widely available especially at tertiary facilities to improve on patient outcomes through early diagnosis.
4. Further research into GCT possibly looking into prospective, randomised, well-controlled, multi-centre studies to look into post-operative adjuvant therapy for patients with advanced stage disease due to their poor prognosis in this study.
5. Improve record keeping and documentation of clinical features in the health records department to help follow up patients for longer periods of time due to the indolent nature of the disease to gain more accurate information into their survival.

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APPENDIX A: VERBAL CONSENT FORM

Dear Respondent,

My name is Dr. Ken Mworia, an Ob/gyn resident at The University of Nairobi. I am undertaking a study on Granulosa cell tumour (GCT) of the ovary, a particular type of cancer that affects women in our country. The purpose of this study is to evaluate the clinical characteristics, histological features and survival of patients managed for GCT of the ovary in Kenyatta National Hospital (KNH).

To complete this work, I need your assistance with information regarding your well-being or the well-being of the patient under your care especially in clarifying some details that may be missing from their file, which will be on a voluntary basis. I wish to state at this point that the authority to access the file was granted by the KNH Ethic Research Committee. The information will only be used for the purpose of this study and will be treated with the utmost confidentiality and privacy. Benefits of participation in this study include playing an integral role in the improved management of women affected by this condition. There is no risk to you in participating in this study as we will use information from your file and will not alter your current management in any way. The correctness and sincerity of the information provided is highly recommended for integrity of the study findings.

You are not under any obligation to comply with this request, but your willingness will be highly appreciated. If you wish to proceed, kindly note that the call may be recorded for purposes of reference. Thank you.

APPENDIX B: DATA COLLECTION FORM

Inconsistencies noted or missing information will be clarified with the patient using the contact information provided in the file.

Abstract the information from the files as guided by the prompts below. Peruse the file to ensure that information is the most current and accurate.

1. Age of patient in years_____
2. Marital status
    - Married
    - Single
    - Divorced
3. Level of education
    - Primary
    - Secondary
    - Tertiary
4. Ethnic background_____
5. Employment status
    - Unemployed
    - Employed
6. Menopausal status
    - Pre-menopausal
    - Postmenopausal
7. Presenting symptoms
    - Postmenopausal bleeding
    - Abdominal swelling
    - Abdominal pain
    - Others (Infertility, hirsutism, breast changes, Precocious puberty)
8. Clinical signs
    - Ascites
    - Anaemia
    - Palpable pelvic mass

9. Initial stage of disease at time of diagnosis?
    - STAGE I

- STAGE II
- STAGE III
- STAGE IV

10. Histology of tumour?
    - AGCT
    - JGCT
    - Unspecified
11. Date when Histological diagnosis was reported_____
12. Date when treatment initiated (Surgery)_____
13. Initial management started outside KNH?
    - Yes
    - No
14. Initial management started within KNH?
    - Yes
    - No
15. Status at last follow up 2 years after diagnosis?
    - Alive
    - Dead
16. Status at last follow up 5 years after diagnosis (Only if diagnosis between 2010, 2011, 2012, 2013, 2014, 2015, 2016)?
    - Alive
    - Dead
17. If alive
    - Date last seen_____
    - Loss to follow up
18. If dead, date of death? _____

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Ref: KNH-ERC/A/44

5th February 2021

Dr. Ken Muthuuri Mworia
Reg. No. H58/10856/2018

Dept. of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Mworia

RESEARCH PROPOSAL - GRANULOSA CELL TUMOUR OF THE OVARY: A DESCRIPTIVE COHORT STUDY IN KENYATTA NATIONAL HOSPITAL, 2012-2018 (P716/12/2020)

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 5th February 2021 - 4th February 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.

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Ref. No.KNH/ERC/Mod&SAE/156 21st June 2021

Dr. Ken Muthuuri Mworia
Reg. No. H58/10856/2018
Dept. of Obstetrics and Gynecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Mworia,

Re: Request for modifications - study titled, 'Granulosa cell tumour of the ovary; A descriptive cohort study in Kenyatta National Hospital, 2012- 2018' (P716/12/2020)

Refer to your communication dated 3rd June, 2021.

Upon review, the KNH-UoN ERC noted the following;

1. Your request to increase the study period from 2012- 2018 to ***2010 - 2020***.
2. It is noted that the calculated study sample size is 73 and you have only been able to retrieve 21 cases forthe period 2012-2018 (7 years). This is 28% of the sample size.
3. Extension of the study period by 4 years is unlikely to achieve your target. A longer period will be more appropriate e.g. from 2020 retrospectively until the desired sample size is achieved, unless there are logistical challenges.

Recommendation

The KNH-UoN ERC recommends that you change the extension to a further period that would allow you achieve the desired sample size as noted above.

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 Chair, Dept. of Obstetrics and Gynecology, UoN
Supervisors: Prof. Zahida Qureshi, Dept. of Obstetrics and Gynecology, UoN
Dr. Wycliffe Musalia, Dept. of Obstetrics and Gynecology, UoN