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CLINICAL CHARACTERISTICS AND OUTCOMES: 10-YEAR REVIEW OF MUCINOUS OVARIAN TUMOURS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A research report submitted in partial fulfilment of the requirements for the degree

Master of Medicine in Obstetrics and Gynaecology

Faculty of Health Sciences

UNIVERSITY OF THE WITWATERSRAND

JOHANNESBURG

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2021

DECLARATION

I, **Kambola Elie Ndala**; hereby declare that this research is of my own work. I am submitting this research for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

.....day of 2021

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Abstract

Background

Primary mucinous ovarian tumours can be benign, borderline, or malignant. Patients with mucinous epithelial ovarian cancer have poor outcomes compared to other epithelial ovarian cancers.

Objectives

This study aimed to describe the clinical characteristics, management and outcomes of mucinous ovarian tumours at Charlotte Maxeke Johannesburg Academic Hospital.

Methods

Patients with mucinous ovarian tumours were selected retrospectively over 10 years. Descriptive quantitative data analysis was carried out.

Results

15/60 (25,00%) had mucinous adenocarcinoma. The overall mean age was 49,95 years (SD±16,53; 95% CI, 45,67-54,22) and in mucinous cystadenocarcinoma was 49,73 years (SD ± 16,08; 95% CI, 40,83-58,64). Cystadenoma were 35(58,33%), cystadenocarcinoma 15(16,67%) and borderline 10(16,67%). 3(5,00%) patients had intraoperative complication and 13(21,67%) had post-operative complications.

Conclusion

Mucinous ovarian tumours affect women of all ages. About 25% are likely to be malignant. Cystadenoma is the commonest subtype and together with borderline tumours, have excellent surgical outcomes.

TABLE OF CONTENTS

DECLARATION ii

ACKNOWLEDGEMENTS iii

ABSTRACT ..... **Error! Bookmark not defined.**

TABLE OF CONTENTS v

LIST OF TABLES ix

LIST OF FIGURES x

ABBREVIATIONS xi

CHAPTER 1: INTRODUCTION AND BACKGROUND OF THE STUDY 1

1.1 Introduction 1

1.2 Background of the study 1

1.3 Problem statement 2

1.4 Aim, objectives, and research questions 2

1.4.1 The Aim of the study 2

1.4.2 Objectives of the study 2

1.4.3 Research questions 3

1.5 Significance of the study 3

CHAPTER 2: LITERATURE REVIEW 5

2.1 Introduction 5

2.2 Classification of mucinous ovarian tumours 5

2.3 Clinical presentation of mucinous ovarian tumours 6

2.4 Histopathological diagnosis of mucinous ovarian tumours 7

2.5 Serum markers 8

2.6 Molecular characteristics of mucinous ovarian carcinoma 8

2.7 Therapeutic approaches in mucinous ovarian tumours 9

2.7.1 Surgery....9
2.7.2 Chemotherapy....10
2.7.3 Targeted therapeutic strategies. 11
2.8 Prognosis 11
2.9 Recurrence rate....11
2.10 Summary 11
CHAPTER 3: RESEARCH METHODOLOGY 122
3.1 Introduction 12
3.2 Research methodology 12
3.2.1 Study design 12
3.2.2 Study population....12
3.2.3 Study setting 12
3.2.4 Sampling method....12
3.2.5 Sample size....13
3.2.6 Inclusion criteria....13
3.2.7 Exclusion criteria....13
3.2.8 Data collection....13
3.2.9 Data analysis....13
3.3 Reliability and validity of the study 14
3.4 Ethical requirements and permission to conduct study....14
3.5 Funding....14
CHAPTER 4: RESULTS AND INTERPRETATION 15
4.1 Introduction 15
4.2 What are the socio-demographic factors of patients with mucinous ovarian tumours in general: Demographics at time of diagnosis. 15
4.2.1 Age....15
4.2.2 HIV and ARV status....16

4.2.3 Family history of cancer 17
4.3 The following results are to answer the research question: what is the clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours: Clinical Presentation, modality of diagnosis; characteristics 19
4.3.1 Clinical presentation 19
4.3.2 Stage at presentation 19
4.3.3. FIGO staging 21
4.3.4 Method of diagnosis 22
4.3.5 Histological characteristics 22
4.3.6 Comorbidities 23
4.3.7 Tumour markers 24
4.3.8 Preoperative workup 30
4.4 To describe the surgical outcomes of malignant mucinous ovarian tumours compared with benign mucinous tumours. 31
4.4.1 Treatment modalities 31
4.4.2 Preoperative and postoperative complications 32
4.5 Death and the survival estimates on patients with malignant lesions 34
4.6 Conclusion 35
CHAPTER 5: DISCUSSION OF RESULTS AND FINDINGS 36
5.1 Introduction 36
5.2 Discussion 37
5.2.1 The socio-demographic factors of patients with mucinous ovarian tumours in general. 36
5.2.2 The clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours 38
5.2.3 The surgical outcome of malignant mucinous ovarian tumours compared with benign mucinous tumours 42
5.2.4 The survival estimates on patients with malignant lesions 44

5.3 Summary 45
CHAPTER 6: CONCLUSION 46
CHAPTER 7: RECOMMENDATIONS.....47
CHAPTER 8: LIMITATIONS OF THE STUDY 48
CHAPTER 9: STRENGH OF THE STUDY.....49
CHAPTER 10: REFERENCES 50
LIST OF ANNEXURES.....58
Annexure 1: Data collection sheet 58
Annexure 2: WHREC clearance letter 64
Annexure 3: Permission letter from office of the hospital CEO, CMJAH 65
Annexure 4: Permission letter from the department of anatomical pathology/NHLS…....66
Annexure 5: Permission letter from the department of obstetrics and gynaecology 67
Annexure 6: NHLS Academic affairs and research permission letter 68

LIST OF TABLES

Table 1 The WHO Classification of mucinous tumours of the ovary 5
Table 2 Differentiating mucinous carcinomas of primary versus metastatic origin. 7
Table 3 Age descriptive statistics for the population study by histology subtypes 16
Table 4 HIV status versus ARVs 16
Table 5 HIV status by histology type 17
Table 6 Family history and type of cancer 17
Table 7 Family history verus affected member 18
Table 8 Association between the ECOG functional score and histology subtypes……..21
Table 9 Work up descriptive statistics of tumour markers 24
Table 10 CA125 Analysis of variance 26
Table 11 CEA Analysis of variance 27
Table 12 CA19-9 Analysis of variance CA 2929
Table 13 Preoperative descriptive statistics 31
Table 13 Treatment modalities by histology subtypes 32
Table 15 Hospital stay in days 33

LIST OF FIGURES

Figure 1 Age of the participants.....15
Figure 2 Types of Cancer.....18
Figure 3 Clinical Presentation.....19
Figure 4 ECOG functional score of women admitted for surgery for mucinous ovarian tumours.. 20
Figure 5 FIGO Staging.....21
Figure 6 Method of diagnosis 22
Figure 7 Histology subtype.....23
Figure 8 Comorbidities 23
Figure 9 Tumour markers at presentation.....24
Figure 10 The tumour marker CA125 analysis of varience.....25
Figure 11 Sensitivity and Specificity of tumour marker CA125 in diagnosing mEOC. 26
Figure 12 Tumour marker CEA.....27
Figure 13 Sensitivity and Specificity of tumour marker CEA in diagnosing mEOC. 28
Figure 14 Tumour marker CA19-9.....28
Figure 15 Sensitivity and Specificity of tumour marker CA 19-9 in diagnosing mEOC.....29
Figure 16 Preoperative Work-up 30
Figure 17 Treatment modalities.....31
Figure 18 Intraoperative and postoperative complications.....33
Figure 19 Readmission 34
Figure 20 Survival estimates.....35

ABBREVIATIONS

α-FP	Alpha Feto-Protein
ALB	Albumin
ARV	Anti-Retroviral
AUC	Area Under the Curve
β hCG	Beta Human Chorionic Gonadotropin
BRCA	Breast Cancer gene
BRAF	B-Raf gene
BSO	Bilateral Salpingo-Oophorectomy
CA 125	Cancer Antigen 125
CA19-9	Carbohydrate Antigen 19-9
CDX2	Homeobox Protein CDX2 gene
CEA	Carcino Embryonic Antigen
CEO	Chief Executive Officer
CI	Confidence Interval
CK5/6	Cytokeratin 5/6
CK7	Cytokeratin 7
CK20	Cytokeratin 20
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CRC	Colorectal Cancer
CREAT	Creatinine

CT scan	Computerized Tomography Scan
DPC4	Deleted in Pancreatic Cancer 4
ECOG	Eastern Cooperative Oncology Group (ECOG) functional status
EGD	Esophagogastroduodenoscopy
EGFR	Epidermal Growth Factor Receptor
ER	Oestrogen Receptors
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOC	Epithelial Ovarian Cancer
FGR2	Fibroblast Growth Factor Receptor 2
FIGO	International Federation of Obstetricians and Gynaecologists
HB	Haemoglobin
HE4	Human Epididymis Protein 4
HER2	Human Epidermal Growth Factor Receptor 2
HGSOC	High-Grade Serous Ovarian Carcinoma
HIV	Human Immunodeficiency Virus
IDS	Interval Debulking Surgery
KRAS	Kirsten Rat Sarcoma
LDH	Lactic Dehydrogenase
LND	Lymphadenectomy
MBT	Mucinous Borderline Tumour
MBOT	Mucinous Borderline Ovarian Tumour
MEK	Mitogen-Activated Protein Kinase

mEOC	Mucinous Epithelial Ovarian Cancer
MOC	Mucinous Ovarian Cancers
MSI	Microsatellite Instability
mTOR	Mammalian Target of Rapamycin
NAC	Neoadjuvant Chemotherapy
NCCN	National Comprehensive Cancer Network
NHLS	National Health Laboratory Service
NHLS/AAR	National Health Laboratory Academic Affair and Research
OCP	Oral Contraceptive Pills
OMC	Ovarian Mucinous Carcinoma
OS	Overall Survival
P	P-value
P16	Protein 16
PARPI	Poly Adenosine diphosphate-Ribose Polymerase Inhibitors
PAS	Periodic Acid-Schiff
PAX8	Paired Box Gene 8
PDS	Primary Debulking Surgery
PET scan	Positron Emission Tomography
PI3K	Phosphatidyl Inositol 3-Kinase
PLT	Platelet
RMI	Risk of Malignancy Index
ROC	Receiver Operating Characteristic
ROCA	Risk for Ovarian Cancer Algorithm

RR	Relative Risk
SATB2	Special AT-rich sequence-binding protein 2
SD	Standard Deviation
Src	Proto-oncogene tyrosine kinase Src
TAH	Total Abdominal Hysterectomy
TKI	Tyrosine Kinase Inhibitor
TM	Tumour Maker
TP 53	Tumour Proteins 53
USO	Unilateral salpingo-oophorectomy
VTE	Venous Thromboembolism
WBC	White Blood Cells count
WHO	World Health Organization
WHREC	University of Witwatersrand Human Research Committee
WT1	Wilms' Tumour 1

CHAPTER 1: INTRODUCTION AND BACKGROUND OF THE STUDY

1.1 Introduction

Primary mucinous ovarian tumours can be benign, borderline, or malignant. Malignant mucinous tumours in the ovary may be primary or metastatic.[1]

It is crucial to accurately diagnose tumours that are metastatic to the ovary since treatment and outcomes may differ significantly from that of primary ovarian carcinoma confined to the ovary. A patient with an early-stage primary mucinous carcinoma will have a 90% 5-year survival, whereas a patient with a metastasis, for example, from a pancreatic cancer primary, may have a life expectancy of <6 months.[2]

Ovarian cancer has the highest mortality of all gynaecological cancers. It is responsible for up to 4,3% of cancer-related deaths in women and is the 8th most common cause of death from cancer in females. It is reported that in 2018 about 295 414 patients developed ovarian cancer worldwide of which 184 799 died.[3]

Mucinous adenocarcinoma accounts for a median of 11,4 % (range: 3,0–38,6%) of the estimated 225 500 women who are annually diagnosed with an epithelial malignancy of the ovary, fallopian tube, or peritoneum worldwide.[3,4]

Historically the incidence of mucinous epithelial ovarian cancer (mEOC) has been about 12 %. With the application of modern histopathological techniques; the true incidence of primary invasive mEOC has seen a decline close to 3 %.[5]

1.2 Background of the study

Mucinous cystadenoma and adenofibroma are benign tumours with gastrointestinal or Mullerian-type mucinous epithelium.[6] They account for approximately 80% of all primary ovarian mucinous neoplasms. Mucinous cystadenomas are far more common than adenofibromas.[7]

Mucinous borderline tumours (MBT) are an architecturally complex non-invasive mucinous neoplasm with gastrointestinal-type differentiation.[6] They are the second most common type of borderline tumour in North America and Europe, but they are the most common subtype in Asia, where they account for about 70% of borderline tumours.[8,9]

Mucinous carcinoma of the ovary is an invasive mucinous neoplasm composed of gastrointestinal-type cells.[6] They account for 3-4% of all primary ovarian carcinomas.[10]

Our study is aimed at reviewing the mucinous ovarian tumours, how they presented, how they were managed and their outcome at Charlotte Maxeke Johannesburg Academic Hospital including a review of how many of these tumours were malignant over a period of ten years.

1.3 Problem statement

Traditionally, primary mucinous ovarian carcinomas have been treated in the same manner as other epithelial ovarian carcinomas. Patients with mucinous ovarian carcinoma have shown to have a poor outcome compared to other ovarian cancers when treated traditionally with the standard taxane and platinum-based chemotherapy.[11]
Novel approaches are therefore needed for the treatment of mucinous ovarian carcinomas.

The low incidence and accrual of mEOC make trials challenging to reach conclusive results and will require international and funded studies.

The difficulty of making a diagnosis of mucinous carcinoma and the poor prognosis of advanced stage mEOC has been reported by many gynaecologic oncologists as illustrated by a retrospective analysis of patients who were entered into the GOG 182 (ICON 5) trial.[12]

1.4 Aim, objectives, and research questions

1.4.1 The aim of the study

The study aimed to describe the clinical characteristics, management and outcomes of mucinous ovarian tumours and their incidence of malignancy at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

1.4.2 Objectives of the study

1. To describe the socio-demographic factors of patients with mucinous ovarian tumours in general.
2. To describe the clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours.
3. To describe the surgical outcome of malignant mucinous ovarian tumours compared with benign mucinous tumours.
4. To calculate the survival estimates on patients with malignant lesions.

1.4.3 Research questions

This study seeks to answer the following research questions:

1. What are the socio-demographic factors of patients with ovarian mucinous tumours in general?
2. What are the clinic-biochemical and pathological profiles of patients with malignant mucinous ovarian tumours?
3. What is the surgical outcome of malignant ovarian tumours compared with benign mucinous tumours?
4. What is the survival estimates on patients with malignant lesions?

1.5 Significance of the study

Mucinous ovarian tumours are rare, and, in our setting, there is a paucity of data on their incidence, clinical presentation, management and the outcome of these tumours. The management of mucinous tumours is still the same as other epithelial ovarian tumours which results in poor outcomes.

Addressing the objectives of this study will add value to the Gynaecological Oncology Unit; Charlotte Maxeke Johannesburg Academic Hospital; the University of the Witwatersrand and the health sectors in understanding the socio-demographic factors of patients with mucinous ovarian tumours in the study setting which can provide awareness in other areas with similar

settings. Furthermore, the health sector will also be aware of the clinic-biochemical and pathological profile of patients with mucinous ovarian tumours in comparison to other related studies presented through literature reviewed by this study. The results of the comparison between surgical outcomes of malignant mucinous ovarian tumours with benign mucinous tumours will further provide evidence if these present significant differences for informative decision making. A further advantage provided by this study is the calculation of the survival estimates on patients with malignant lesions which provides the beneficiaries of the study with awareness of time estimates.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

As a result of the application of modern histopathological techniques, the incidence of primary invasive mucinous epithelial carcinoma has fallen over recent years from~12% to~3%.[5]

This chapter presents the literature review related to mucinous epithelial ovarian cancer presented by other authors to assess the evidence presented, identify gaps, and align to what this study seeks to achieve.

This chapter presents the classification of mucinous ovarian tumours, their clinical and molecular characteristics and the prognosis of the mucinous ovarian tumours.

2.2 Classification of mucinous ovarian tumours

The 2020 WHO Classification of Tumours, 5th Edition, Female Genital Tumours subdivides mucinous ovarian tumours into mucinous cystadenoma, mucinous adenofibroma, mucinous borderline tumours, and mucinous adenocarcinoma.[6]

Table 1 The WHO classification of mucinous tumours of the ovary.[6]

Type	Subtype
Benign	Mucinous cystadenoma Mucinous adenofibroma
Borderline	Mucinous borderline tumour
Malignant	Mucinous adenocarcinoma.

Mucinous cystadenoma and adenofibroma: The association of some of these tumours with dermoid cysts suggest a germ cell origin. Some arise in association with Brenner tumours.[6] The reported association range from 1% to 16%. Seidman and colleagues found in one study that a total of 25% of tumours with a mucinous component contained a Brenner component,

and 16% of tumours with a Brenner component contained a mucinous component.[13] Mucinous cystadenomas display no cellular atypia and there is no stromal invasion. Generally, they are large tumours, usually unilateral, with a smooth or bosselated surface and are lined by a single layer of columnar cells with abundant intracellular mucin.[14] Adenofibromas are usually smaller, predominantly solid, and punctuated with small cysts.[7,15]

Mucinous borderline tumour: The mean size is about 20cm, with some cases as large as 50 cm.[16] The tumours are nearly always unilateral, multiloculated with smooth walls and mucinous contents. These tumours contain multiple cysts lined by gastrointestinal-type mucinous epithelium showing variable degrees of stratification, tufting, and villous filiform papillae. There is generally low-grade nuclear atypia. Epithelial proliferation must account for >10% of the epithelial volume for the tumour to be qualified as MBT.[17]

Mucinous cystadenocarcinoma: The tumours are typically large, unilateral, solid, and cystic, with an intact and smooth outer surface and mucoid contents; however, some tumours may rupture and be associated with adhesions. There is often a continuum of architectural and cytological atypia that includes benign, borderline, and carcinomatous areas.[6]

2.3 Clinical presentation of mucinous ovarian tumours

Mucinous ovarian tumours generally occur in young women with 83% stage 1 at the time of diagnosis and 17% stage 2 or higher.[18] Like for all the epithelial ovarian tumours the clinical presentation of mucinous ovarian tumours may be acute, sub-acute, or in some cases, found incidentally during an examination, imaging, or surgery for another indication. Most commonly, they present in a sub-acute fashion (e.g., pelvic, or abdominal pain, bloating, and urinary urgency or frequency). Patients who present in an acute fashion are typically those with advanced disease who present with a condition that requires urgent care and evaluation (e.g., pleural effusion, bowel obstruction, and ascites.)[19,20,21]

2.4 Histopathological diagnosis of mucinous ovarian tumours

The clinical importance of a correct histopathological diagnosis of an ovarian tumour cannot be underestimated. Patient outcomes can differ greatly depending on the true underlying diagnosis: a patient with primary ovarian carcinoma confined to the ovary will have a 90% 5-year survival, whereas a patient with a metastasis, for example, from a pancreatic cancer primary, may have a life expectancy of <6 months.[1,22]

Table 2 Differentiating mucinous carcinomas of primary versus. metastatic origin.[23]

	Primary	Metastatic
Pathological pattern	Intracellular mucin (>50%), in at least 90% of tumour cells. Complex papillary pattern	Abundant extracellular mucin, in 50% or greater tumour volume. Nodular pattern
Involvement	Coexistence of borderline/benign mucinous component. Expansile pattern of invasion	Ovarian surface involvement. Hilar involvement. Vascular invasion. Extensive infiltrative pattern of invasion
Size and distribution	Unilateral Size >10 cm	Bilateral Size <10 cm
Markers	CA125CEA >25	Elevation may be present, although less than in colorectal primary cancers
Molecular alterations	*KRAS* mutations: 43% *BRAF* mutations: 0%*HER2* amplification: 18%	*KRAS* mutations: 30% *BRAF* mutations: 20% *HER2* amplification: <1%

Stage at diagnosis: 83% of ovarian mucinous carcinomas are diagnosed at Stage 1 compared to 49% of serous ovarian carcinomas.[18]

Laterality and size: 79% are diagnosed with a mean size of 18 cm and are unilateral.[24]

Lymph nodes and metastasis: Retroperitoneal lymph nodes assessment is part of the staging surgery in all EOCs.[25] It is understood that the chance of lymph node involvement in grossly confined non-mucinous epithelial carcinoma of the ovary is 20–30%. The role of routine systematic lymphadenectomy in early-stage MOC is, however, debatable.[26]

2.5 Serum markers

When combined with standard imaging techniques, serum tumour markers are useful in the diagnosis and monitoring of ovarian cancer. Several serum tumour markers (STMs)—including cancer antigen 125 (CA125), human epididymis protein 4 (HE4), cancer antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA)—have been used as a non-invasive method of identifying ovarian cancer in conjunction with imaging. CA125 is the most commonly used STM; its level may be elevated in several types of ovarian cancer, including epithelial cell tumours, carcinosarcoma, teratomas, and secondary ovarian malignancies.[26] CEA is most commonly associated with mucinous ovarian cancers. CEA is more elevated in mucinous ovarian carcinomas than in non-mucinous (88% VS 19%).[27,28] An elevated level of CA 19-9 is associated with clear cell tumours, teratomas, and secondary malignancies. A revision of the mucinous cancer algorithm by Maeda-Taniguchi and colleagues has found that combining serum biomarkers CA125 and CA19-9 further improved the positive predictive values of tumour classification.[29]

2.6 Molecular characteristics of mucinous ovarian carcinoma

The predominant mutation is in *KRAS* where a mutation is found in 40%–50% of patients.[30] *HER2* gene and *p53* gene mutation also play a significant role in mEOC.[31]

Mucinous ovarian tumours develop on a continuum from benign to preinvasive (borderline) carcinoma to mucinous carcinoma. *KRAS* mutations are an early event, whereas other

oncogenic alterations (*HER2* amplifications or *TP3* mutations) may be acquired later during malignant transformation.[32]

2.7 Therapeutic approaches in mucinous ovarian tumours

2.7.1 Surgery

The choice of surgery modalities is multifactorial and will be determined by the histological subtype, stage of the disease, age, and fertility desire. The gold standard surgical management of all EOCs, including MOC, is a staging procedure for early disease and cytoreductive surgery for advanced disease.[33,34,35]

In patients with advanced cancer, it is recommended that initial surgical treatment includes maximal primary debulking surgery (PDS) aimed at complete removal of all macroscopic tumours (complete surgery including the contralateral ovary and the uterus) in addition to staging.[36] On the other hand, if maximal tumour reduction is considered to be impossible to accomplish by initial surgery, performing interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) is the preferred treatment option because non-inferiority of the overall survival (OS) has been confirmed by several Phase III randomized trials comparing PDS with IDS after NAC.[37,39]

Fertility sparing staging (FSS): MOC is the most prevalent epithelial carcinoma among women of reproductive age with 80% of all MOC presenting as stage I.[39] FSS is frequently addressed during the management of such pathology and is safe for stage I MOC with an excellent prognosis.[40]

Appendectomy: Many experts recommend appendectomy for mucinous ovarian cancer. Lin and colleagues in one retrospective study after assessing the role of appendectomy in the management of mucinous ovarian tumours concluded that the appendix should not be removed unless it is grossly abnormal, as there was no abnormal pathology found in the normal-appearing appendix. They, therefore, recommended that careful intraoperative inspection of the appendix is mandatory, but a normal-looking appendix should not be routinely removed.[41]

Lymphadenectomy: Retroperitoneal lymph nodes assessment is part of the staging surgery in all EOCs. The role of routine systematic lymphadenectomy in early-stage MOC is, however, debatable.[25]

Laparoscopic techniques: can be advised in the hands of a skilled surgeon. Short post-operative recovery, early return to work, less blood loss, less pain, fewer adhesions, and good cosmetic outcomes are some of the advantages associated with laparoscopic techniques. The drawbacks are cyst rupture (33,9% laparoscopy versus 12,4% laparotomy), higher recurrence rate, concerns about port metastases and improper staging. In the case of an intraperitoneal spill, the laparoscopic procedure should immediately be converted into laparotomy.[42]

2.7.2 Chemotherapy

The current standard of care in managing all EOCs, including MOC, is surgical staging for early disease and cytoreductive surgery for advanced-stage disease followed by platinum-based chemotherapy.[32,33]

Apart from Stage 1 mEOC which has excellent prognosis (90% five-year survival) with surgery alone,[43,44] advanced mEOC have a poor outcome compared with HGSOC when treated with the standard platinum-based chemotherapy.[45]

Due to the biological and molecular similarities of MOC and mucinous CRC, GI chemotherapy protocols have been proposed as an alternative to the standard gynaecology regimen. To date, there have been no successful prospective phase II or III randomized clinical trials directed specifically to MOC.[25]

The American Cancer Society National Comprehensive Cancer Network (NCCN) guidelines recommend that stage 1 mEOC be treated by surgery alone (no need for chemotherapy as the survival rate is excellent) and stage II-IV mEOC be treated with adjuvant therapy (3-6 cycles of taxane/carboplatin or 5-fluorouracil/oxaliplatin or capecitabine/oxaplatin).[28,46]

2.7.3 Targeted therapeutic strategies.

The recently proven efficacy of PARPIs (poly adenosine diphosphate-ribose polymerase inhibitors) in managing non-mucinous type EOC is a milestone in ovarian cancer management. Unfortunately, PARPIs have no role in the management of MOC as these tumours are not associated with *BRCA* mutations or homologous recombinant deficiency.(25)

The anti-epidermal growth factor receptor (anti-*EGFR)* monoclonal antibody therapy (cetuximab) is promising in vitro. It shows anti-proliferative activity on mEOC cell lines not harbouring *KRAS* mutations. Its value may be limited to *KRAS* wild-type cases. Further data is required. Trastuzumab, a *HER2* monoclonal antibody, showed benefits to OS in *HER2*-positive gastric carcinoma. Some case reports reported the successful use of trastuzumab in combination with chemotherapy in a few patients with MOC who had *HER2* amplification. Nevertheless, more data on MOC is needed on anti-*HER2* therapy in *HER2*-amplified.[25,46]

2.8 Prognosis

Although survival for early-stage mucinous and serous tumours is similar, survival for advanced-stage mucinous neoplasms is inferior to that of serous carcinomas.[47]
Median survival for Stage III/IV disease is 15 months compared to 41months for serous histology.[11]

2.9 Recurrence rate

Intraepithelial (non-invasive) mucinous ovarian carcinoma, FIGO Stage 1, has a recurrence rate of 5,8%.[48] Invasive mucinous carcinoma with an infiltrative pattern has a more aggressive course than mucinous carcinoma with an expansile pattern.[49] About 80% of OMCs with infiltrative invasion are stage I, 20% of which recur. Recurrences tend to occur within 3 years of diagnosis and do not respond to chemotherapy or radiotherapy.[23]

2.10 Summary

Historically, primary mucinous ovarian carcinomas have been treated in the same manner as other epithelial ovarian carcinomas. Patients with mucinous ovarian carcinoma have proven to have poor outcomes compared to other ovarian cancer when treated traditionally with the standard taxane and platinum-based chemotherapy thus novel approaches are needed for mucinous ovarian carcinomas.

The low incidence and accrual of mEOC make trials challenging to reach conclusive results.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction

The research methodology provides specific procedures or techniques used to identify, select, process, and analyse information about a topic is presented in this chapter. This includes the research design, defining the target population of the study, the study setting, sampling method and sample size, inclusion and exclusion criteria considered for the study, data collection methods and analysis; reliability and validity of the instruments used to collect the data.

3.2 Research methodology

3.2.1 Study design

The study was a descriptive retrospective review, using medical records of patients at Charlotte Maxeke Johannesburg Academic Hospital Gynaecological Oncology Clinic.

3.2.2 Study population

Women with a histologically confirmed diagnosis of ovarian mucinous cystadenoma, mucinous borderline ovarian tumours and mucinous cystadenocarcinoma managed at CMJAH were selected retrospectively over 10 years.

3.2.3 Study setting

Women with a histologically confirmed diagnosis of ovarian mucinous cystadenoma, mucinous borderline ovarian tumours and mucinous cystadenocarcinoma managed at Charlotte Maxeke Johannesburg Academic Hospital (Gynaecological Oncology).

3.2.4 Sampling method

All women with confirmed mucinous ovarian tumours managed at CMJAH were selected retrospectively over 10 years (from January 2008 to December 2017).

3.2.5 Sample size

This was a retrospective study based on a period where histology reports were available and included all patients who had surgery for mucinous ovarian tumours for that time period. Hence, there was no sample size calculation done.

3.2.6 Inclusion criteria

All patients with a histologically confirmed diagnosis of mucinous ovarian tumour (benign and malignant).

3.2.7 Exclusion criteria

Patients with incomplete histology reports and theatre notes were excluded. Patients who were referred to CMJAH for adjuvant therapy or management of complications but not primarily operated at CMJAH.

3.2.8 Data collection

Data were retrieved from the patients' records and information was transferred to a data collection sheet (Appendix A). Histology and immunohistochemistry results were obtained from patients' files. If not available in the files they were obtained from the National Health Laboratory Services (NHLS) electronic records.

3.2.9 Data analysis

The study employed quantitative data analysis techniques. Descriptive analysis of the data was carried out. Descriptive statistics entailed frequency and percentage in categorical variables and were presented by tables and graphs. Continuous variables were summarized by the mean, standard deviation and median, and their distribution was illustrated by means of histograms. Data analysis was carried out using Stata and SPSS software. The 5% significance level was used to measure significance. Precision was managed by using 95% confidence intervals.

The Chi-Square (X^2) test was used to assess the association between tumour groups and demographic and clinical characteristics, staging, histological findings of the ovarian tumour.

Cox proportional hazards regression was used to analyse the relationship between the treatment group and disease recurrence.

Survival data for a period of study was presented by the Kaplan-Meier survival curves and survival estimates. The survival status of the patient was determined as alive or dead at the time of the last recorded follow-up visit.

Surgical outcomes were assessed in terms of operative mortality, complication rates, length of stay, readmission rates and patient satisfaction.

3.3 Reliability and validity of the study

The data was collected retrospectively thus reliability does not apply as the information captured in the study template can be compared to what is in the hospital files for corrections. Validity was determined in this study by applying the quantitative techniques to analyse and test the results ensuring that the study met the objective of what it was intended to achieve.

3.4 Ethical requirements and permission to conduct study

Permission to use data at Gynaecological Oncology Unit was granted by the Head of Obstetrics and Gynaecology Department and by the office of the Chief Executive Officer (CEO) of the Charlotte Maxeke Johannesburg Academic Hospital and (See Annexure1 and 2 respectively). This study was approved by the University of Witwatersrand Human Research Ethics Committee (WHREC) (Clearance certificate number M1911117) (See Annexure 3). The study also got approval from the Head of the Department of Anatomical Pathology and the National Manager of Academic Affairs and Research at the National Health Laboratory Service (NHLS-AARMs) to access their databases (See Annexure4 and 5 respectively).

3.5 Funding

The study did not require funding. There was no equipment purchased and all other incidental costs were borne by the researcher.

CHAPTER 4: RESULTS AND INTERPRETATION

4.1 Introduction

This chapter presents the results and interpretation of the study. These are achieved through data collected using the methods presented in the preceding chapter. Analyzing these results will ensure that the objectives of the study are met and that the research questions are answered. A p-value of 0,050 was applied to test the level of significance.

The following results seek to answer the research question:

4.2 What are the socio-demographic factors of patients with mucinous ovarian tumours in general: Demographics at time of diagnosis.

4.2.1 Age

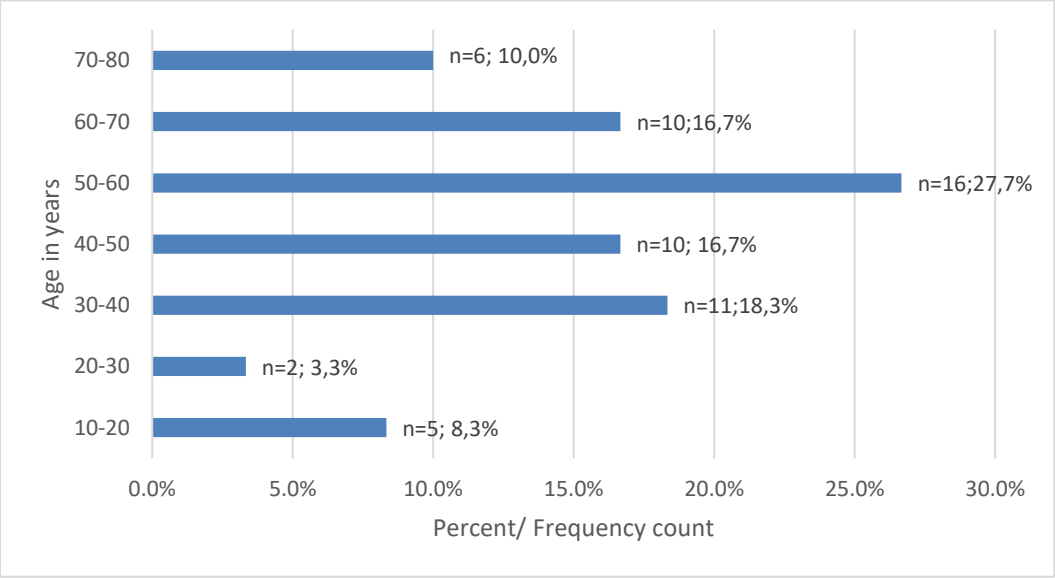


Figure 1 Age of the patients

Figure 1 depicts the age groups of patients. Results show that majority of participants were above the age of 50 (53,40% of patients) compared to 46,60% of patients that were below the age of 50. Most of these patients were between 50-60 years of age group (n=16; 27,70%) followed by 11(18,30 %) the patients within the age group of 30-40 years. Those within the age of 40-50 and 60-70 years of age contributed with 10(16,70%) patients respectively while the 10-20 years of age were 5(8,30%) patients, and the least was 2(3,30%) patients within the age group of 20-30 years.

Table 3 Age descriptive statistics for the population study by histology subtypes

	N	Mean	Confidence (-95%)	Confidence (95%)	Median	Min	Max	SD.	Std Error
Cystadenoma	35	49,06	44,00	54,12	52	13	76	16,00	2,70
MBT	10	53,40	48,18	58,62	57	19	80	20,14	6,36
Cystadenocarcinoma	15	49,73	40,83	58,64	50	18	78	16,08	4,15
Age (All)	60	49,95	45,67	54,22	52	13	80	16,53	2,13
				Multiple R=0. P=0,761.					

Table 3 shows that from the study sample of 60(100,00%) patients, the mean age of the study population was 49,95(SD ± 16,53) years with a range of 13 years as minimum age and to 80 years as the maximum age (95% CI, 45,67-54,22). The mean age of patients with mucinous cystadenoma was 49,06(SD±16,00) years with a range of 13 years as minimum age to 76 years as the maximum (95%CI, 44,00-54,12). The mean age of patients with mucinous borderline tumours was 53,40(SD±20,14) years with a range of 19 years as minimum age to 80 years as the maximum (95%CI, 48,18-58,62). The mean age of patients with mucinous adenocarcinoma was 49,73(SD±16,08) years with a range of 18 years as minimum age to 78 years as the maximum (95%CI, 40,83-58,64). The p-value was 0,761 and we conclude that this does not reach the statistical significance.

4.2.2 HIV and ARV status

Table 4 HIV status versus ARVs

		ARVS		
		NO	YES	TOTAL
HIV STATUS	Negative	52	0	52
		86,67%	0,00%	86,67%
	Positive	0	8	8
		0,00%	13,33%	13,33%
	Total	52	8	60
		86,67%	13,33%	

Results in Table 4 show that there were 52(86,67%) patients who were HIV negative and not on ARVs compared to 8(13,33%) of patients who were HIV positive and on ARVs. All the patients who were HIV positive 8(13,33%) patients were on antiretroviral drugs (ARVs).

Table 5 HIV status by histology type

		HISTOLOGY SUBTYPES			
		MUCINOUS BORDERLINE	MUCINOUS CYSTADENOMA	MUCINOUS CYSTADENOCARCINOMA	Total
HIV STATUS	NEG	9	29	14	52
		15,00%	48,33%	23,33%	86,67%
	POS	1	6	1	8
		1,67%	10,00%	1,67%	13,33%
	Total	10	35	15	60
		16,67%	58,33%	25,00%	
Pearson Chi-square: 1,112, df=2, p=0,573					

Results in Table 5 show that there is no significant association between HIV status and the histology subtype (Pearson Chi-square: 1,112; p-value 0,753). This shows that there is not enough evidence that HIV status is associated with any of the histology subtypes.

4.2.3 Family history of cancer

Table 6 Family history and type of cancer

		Type of Cancer					
		NONE	OVARY	COLON	ENDOMETRIAL	BREAST	TOTAL
FAMILY HISTORY OF CANCER	NO	54	0	0	0	0	54
		90,00%	0,00%	0,00%	0,00%	0,00%	90,00%
	YES	0	3	1	1	1	6
		0,00%	5,00%	1.67%	1,67%	1,67%	10,00%
	Total	54	3	1	1	1	60
		90,00%	5,00%	1,67%	1,67%	1,67%	
By Type of cancer: Chi-square: 60,000, df=4, p=0,000							

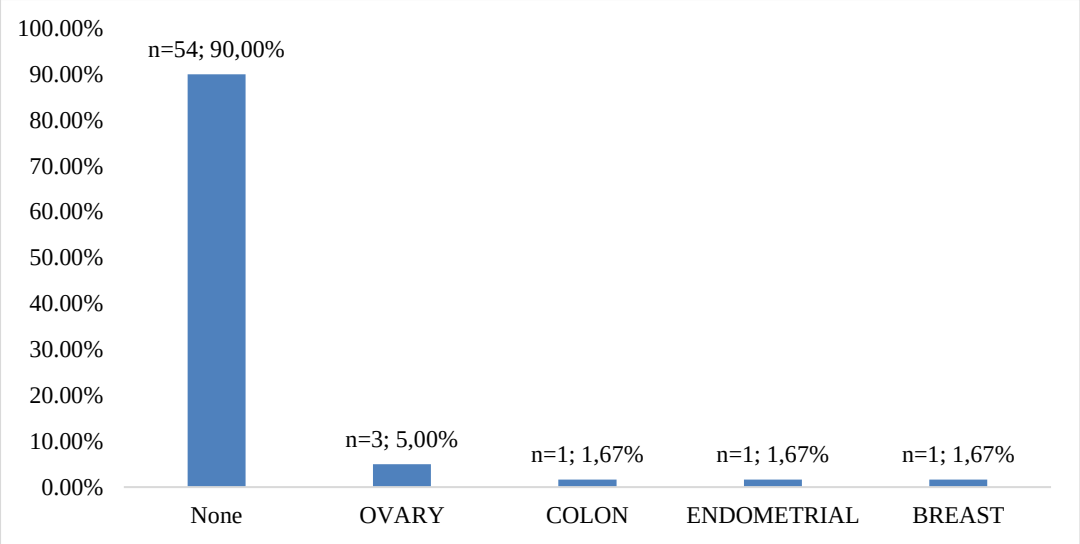


Figure 2 Types of cancer

Table 6 and figure 2 show that there were six (10%) patients that had a positive family history of a family member affected by cancer. Of the six family members affected 3 members representing 3(5,00%) patients had an ovarian cancer while 1 member representing 1 (1,67%) patient had colon cancer, endometrial cancer, and breast cancer respectively. There is strong evidence to suggest that there is an association between mucinous tumours and family history (Chi-square: 60,000, df=4, p=0,000). Of the 15 patients diagnosed with mucinous cystadenocarcinoma, 3 patients had a family history of cancer.

Table 7 Family history versus affected member

		AFFECTED FAMILY MEMBER				
		None	SISTER	GRAND MOTHER	MOTHER	Total
FAMILY HISTORY OF CANCER	NO	54	0	0	0	54
		90,00%	0,00%	0,00%	0,00%	90,00%
	YES	0	4	1	1	6
		0,00%	6,67%	1,67%	1,67%	10,00%
	Total	54	4	1	1	60
		90,00%	6,67%	1,67%	1,67%	
Chi-square: 50,181 df=3 p=0,000						

Table 7 shows that the family members of the six 6(10,00%) patients who had a positive family history of cancer were sisters represented by 4(6,67%) patients; grandmother represented by 1(1.67%) patient and mother represented by 1(1,67%) patient. The strong evidence of an association is due to a Chi-square value of 50,18 with a p-value of 0,000. Of

the 15 patients diagnosed with mucinous cystadenocarcinoma, 3 patients had a positive family history of cancer (sister, mother, and grandmother respectively). There were 2 patients with mucinous cystadenoma that had a positive family history of cancer and 1 patient with mucinous borderline tumour had a positive family of cancer.

4.3 The following results are to answer the research question: what is the clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours: Clinical presentation, modality of diagnosis; histological characteristics

4.3.1 Clinical presentation

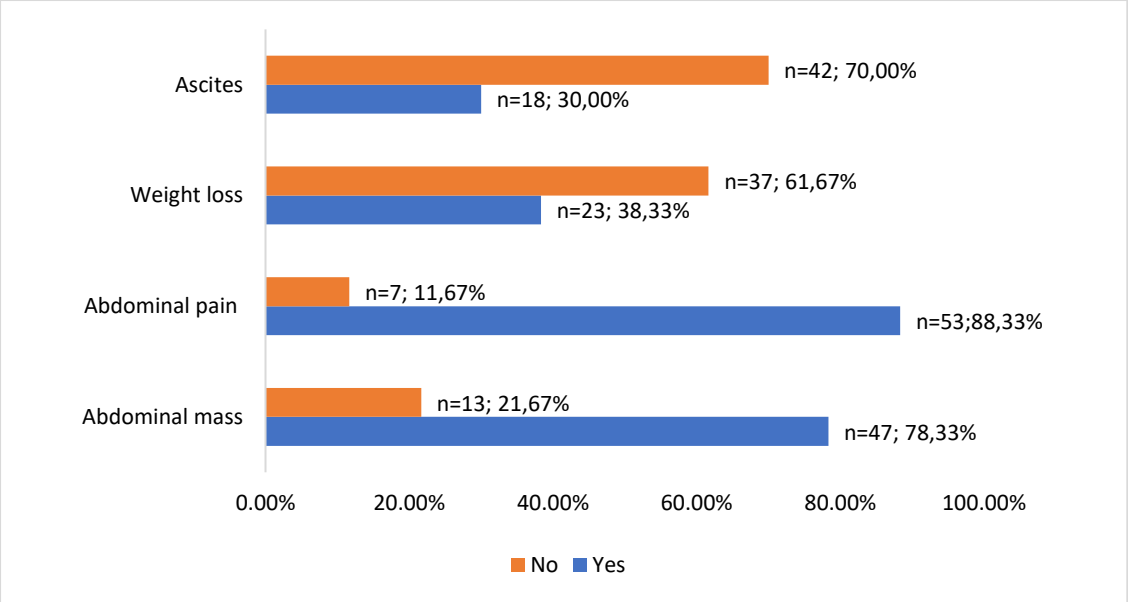


Figure 3 Clinical presentation

Figure 3 shows that most patients at presentation complained about abdominal pain. This is represented by 53(88,33%) patients which includes all 15 patients diagnosed with mucinous cystadenocarcinoma; followed by abdominal mass in 47(78,33%) patients which includes 13 of the 15 patients diagnosed with mucinous cystadenocarcinoma. Patients with weight loss were seen in 23(38,33%) of women and of these patients 14 of 15 had mucinous cystadenocarcinoma. Ascites was present in 18(30,00%) patients of which 14 had mucinous cystadenocarcinoma. Results show that between clinical presentation and histology types, there is a significant association (Chi-square: 38,956; df=2; p=0,000).

4.3.2 Stage at presentation

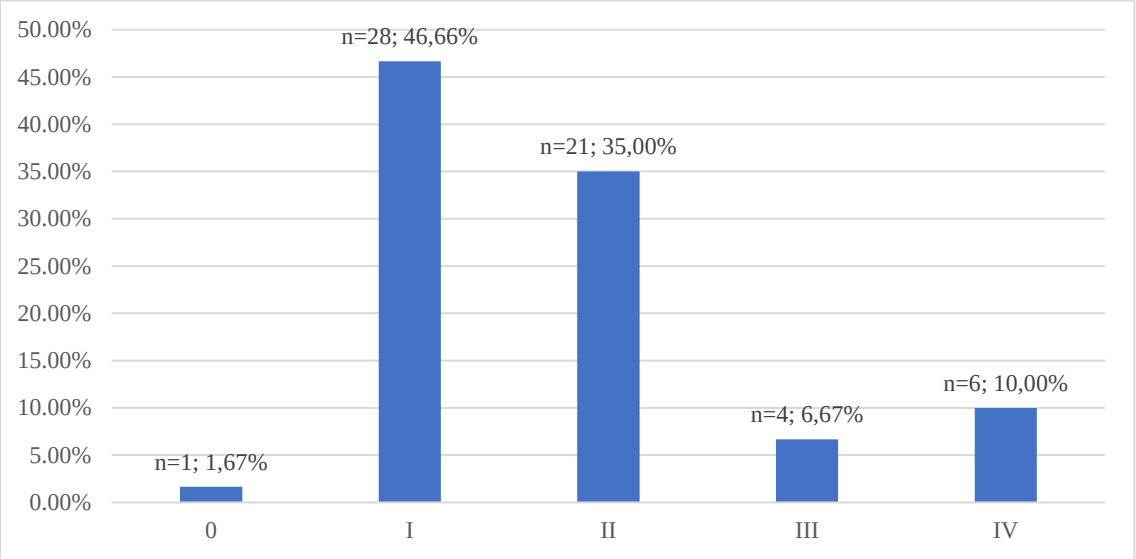


Figure 4 ECOG functional score of women admitted for surgery for mucinous ovarian tumours.

The following Eastern Cooperative Oncology Group (ECOG) stages were noted: 1(1, 67%) patient was assessed as being Stage 0, 28(46,66%) patients were assessed as Stage I, 21(35,00%) patients as Stage II, 4 (6,67%) patients as Stage III, and 6(10,00%) patients as Stage IV. Of the 15 patients diagnosed with mucinous cystadenocarcinoma there was none assessed as being Stage 0, 1 patient assessed as Stage I, 5 patients as Stage II, 4 patients as Stage III, and 5 patients as Stage IV.

Table 8 Association between the ECOG functional score and histology subtypes

Histology subtypes	ECOG stages					
	0	I	II	III	IV	Total
Cystadenoma	1(1,67%)	22(36,67%)	12(20,00%)	0(0,00%)	0(0,00%)	35(58,3%)
Mucinous borderline tumours	0(0,00%)	5(8,33%)	4(6,67%)	0(0,00%)	1(1,67%)	10(16,67%)
Cystadenocarcinoma	0(0,00%)	1(1,67%)	5(8,33%)	4(6,67%)	5(8,33%)	15(25,00%)
Total	1(1,67%)	28(46,66%)	21(35,00%)	4(6,67%)	6(10,00%)	60(10,00%)

Pearson chi2(8) = 31,6 Pr=0,000

Likehood-ratio chi2(8) = 34.196 Pr=0,000

Fisher's exact = 0,000

Fisher's exact test p=0,000

Table 8 shows the calculation of the association between the ECOG functional score and histological subtypes. There is significant association between the ECOG functional score and the histological subtypes (Fisher's exact test p=0,000 which is less than 0,050).

4.3.3. FIGO staging

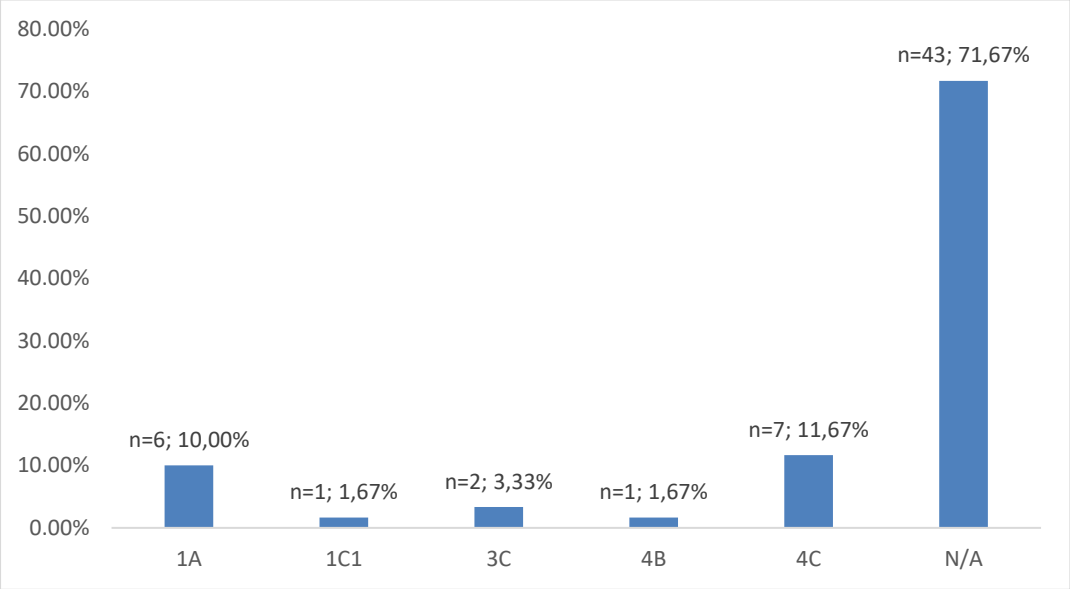


Figure 5 FIGO staging

The FIGO staging of these patients showed that 43(71,67%) patients had no applicable stage (not documented in patients files) while stage I was represented by 7(11,67%) patients, stage IV was represented by 8 (13,34%) patients, and stage III was represented by 2(3,33%) patients. Of the 15 patients diagnosed with mucinous cystadenocarcinoma, the majority were in FIGO stage IVC affecting 7 patients while 3 of 15 patients were in stage IA, 1 patient was in stage IVB and 2 of 15 patients were in FIGO stage IIIC. Results show that there is strong evidence to conclude an association between histology type and FIGO stage (Chi-square: 55,232; df=10; p=0,000).

4.3.4 Method of diagnosis

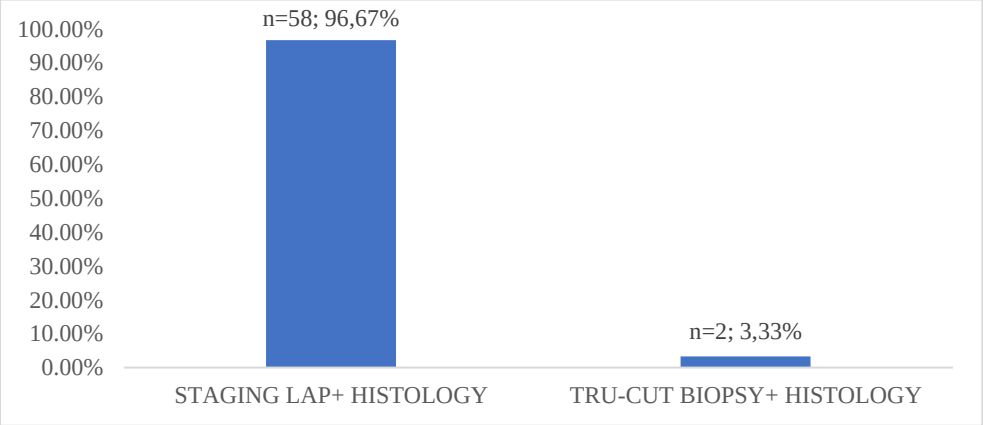


Figure 6 Method of diagnosis

All the 60 (100%) patients were diagnosed through a histology assessment of which 58(96,67%) histologies were following a staging laparotomy, and 2(3,33%) histologies were following a sonar guided Tru-cut biopsy.

4.3.5 Histological characteristics

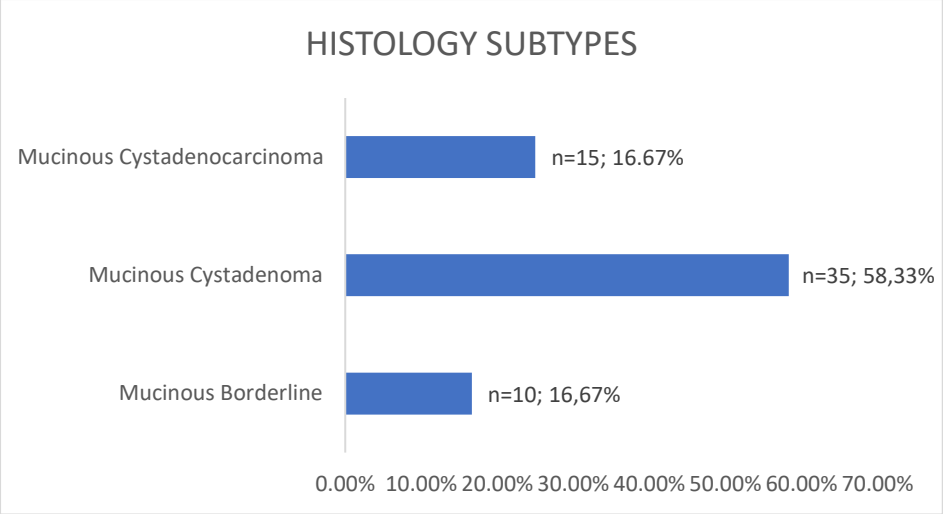


Figure 7 Histology subtypes

The figure 7 shows that the subtype common to most of the patients was mucinous cystadenoma in 35(58,33%) patients, followed by mucinous cystadenocarcinoma in 15(16,67%) patients, then mucinous borderline tumours in 10(16,67%) patients.

4.3.6 Comorbidities

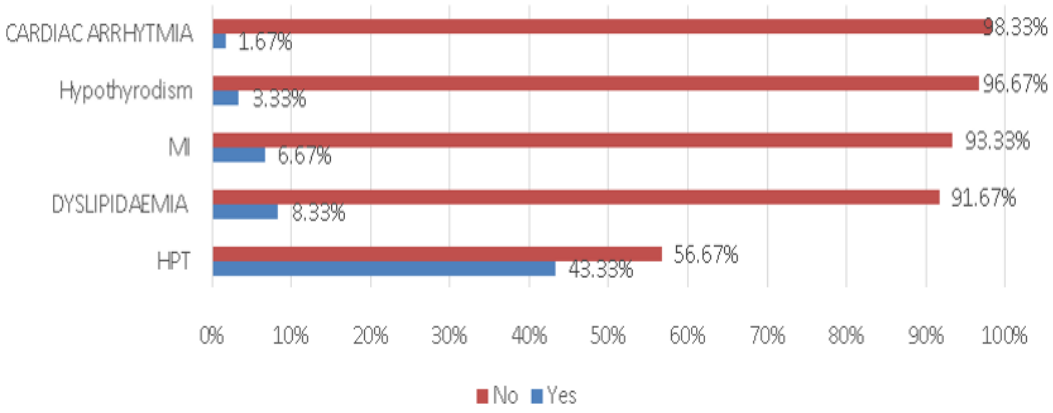


Figure 8 Comorbidities

Results in Figure 8 show that chronic medical comorbidities were hypertension in 26(43,33%) patients, dyslipidaemia in 5(8,33%) patients, myocardial infarction in 4(6,67%) patients, hypothyroidism in 2(3,33%) patients, and cardiac arrhythmia in 1(1,67%) patient.

4.3.7 Tumour markers

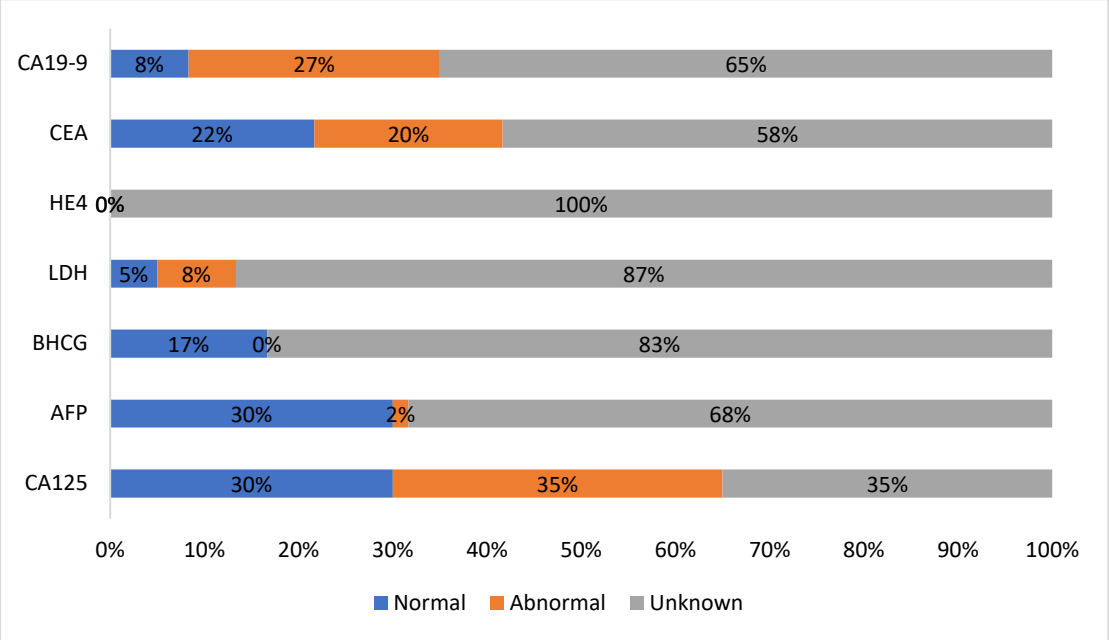


Figure 9 Tumour markers at presentation

In 35 %, CA 125 values were abnormal and unknown in 35%. In 2% of patients AFP values were abnormal and unknown in 68%. bHCG markers were unknown in 83 % and in the remainder, the values were normal., LDH values were abnormal in 8% of patients and unknown in 87%. There were no patients with abnormal HE4 marker. In 20% of patients, CEA values were abnormal. However, it was unknown in 58% of patients. CA 19-9 values were abnormal in 27% of patients, and unknown in 65%.

Table 9 Work up descriptive statistics of tumour markers

Descriptive statistics	*CA125*	*AFP*	*LDH*	*CEA*	*CA19-9*
Mean	127,90	12,32	626,38	29,87	346,45
Standard Error	46,75	7,85	264,01	10,46	112,91
Median	41,9	2,5	389	4,4	112
Mode	34	2,5	244	1,1	
Standard Deviation	291,97	34,20	746,74	52,30	517,40
Range	1787	149,4	2235	218,5	1643,8
Minimum	5	0,6	210	0,5	1,2
Maximum	1792	150	2445	219	1645
Count	39	19	8	25	21
Confidence Level (95,0%)	94,645	16,484	624,293	21,588	235,519

Table 9 shows that the mean of the tumour marker CA125 was abnormal on average (127,90>35 U/mL) with a minimum of 5 U/mL and 1797 U/mL as the maximum, and the most frequent CA125 level was 34 U/mL. The difference between the mean and the median is the outliers presented by high CA125 found on a few of the patients. There was however a high variation of CA 125 for the patients. The majority of patients had on average normal AFP (12,32 ng/mL<100) while LDH (626 U/L >333), CEA (29,8>5ng/mL), and CA19-9 (349,45 U/mL >39) were on average abnormal.

Tumour marker CA 125

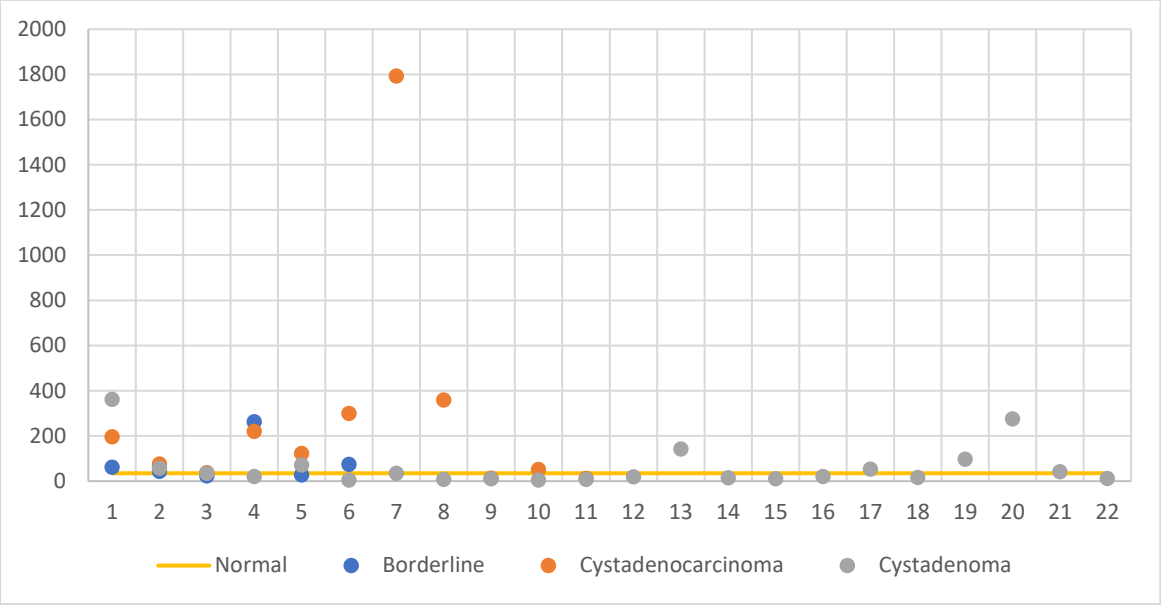


Figure 10 Tumour marker CA125

The above figure shows tumour marker CA 125 by histology subtypes of mucinous tumours. The table below (Table 10) shows a positive correlation of 48% between the marker levels and degree of malignancy. There is a consistent upward trend from benign (mucinous cystadenoma) through mucinous borderline tumours to malignancy (mucinous cystadenocarcinoma). The CA 125 mean values were 59,94 U/mL for cystadenoma, 81,65 U/mL for borderline tumours and 289,04 U/mL for cystadenocarcinoma. The CA 125 correlation between benign and malignancy was not statistically significant (p>0,050).

Table 10 Tumour marker CA 125 analysis of variance

Anova: Single Factor						
Groups	*Count*	*Sum*	*Average*	*Variance*		
Borderline	6	489,9	81,65	8188,615		
Cystadenocarcinoma	11	3179,5	289,0455	262295,4		
Cystadenoma	22	1318,8	59,94545	8349,771		
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	400072,9	2	200036,4	2,53635	0,093215	3,259446
Within Groups	2839242	36	78867,83			
Total	3239315	38				

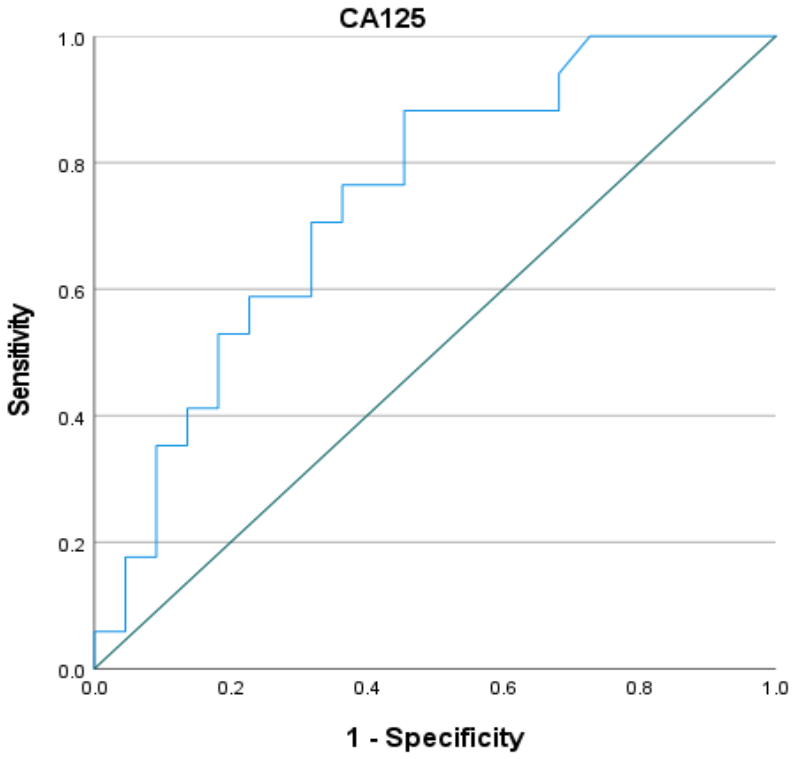


Figure 11 Sensitivity and Specificity of tumour marker CA125 in diagnosing mEOC.

The Receiver Operating curve (ROC) of tumour marker CA 125 was used to calculate sensitivity and specificity for diagnosing mEOC. The area under the curve (AUC) is 0,742(95% CI). This makes the tumour marker CA 125 an acceptable tool for the diagnosis of malignancy. Hosner and colleagues gives the following general guidelines for applied logistic regression: AUC = 0,50 No model discrimination; 0,50 < AUC < 0,70 Poor

discrimination; 0,70 < AUC < 0,80 Acceptable discrimination; 0,80 < AUC < 0,90 Excellent discrimination; AUC > 0,90 Superior discrimination.[64]

Tumour marker CEA

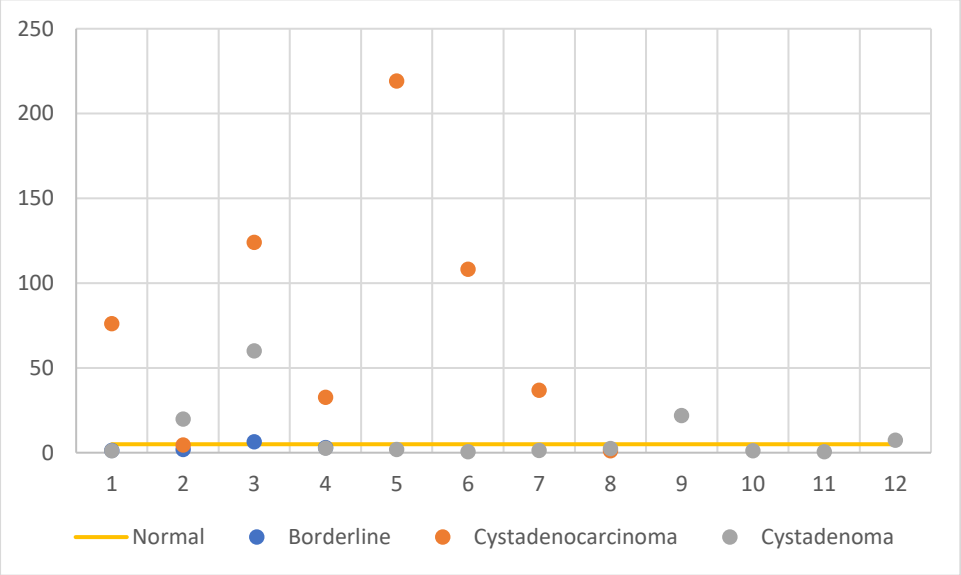


Figure 12 Tumour marker CEA

Figure 12 and table 11 show that the tumour marker CEA had a significant difference between benign tumours (cystadenoma and borderline tumours); however, cancer (cystadenocarcinoma) showed remarkably high levels of CEA (p=0,008). The CEA mean values of 3,10 ng/mL for borderline tumours was normal compared to 10,21 ng/mL for cystadenoma, and 60,44 ng/mL for cystadenocarcinoma which were above the normal range.

Table 11 CEA Analysis of variance

Anova: Single Factor						
Groups	*Count*	*Sum*	*Average*	*Variance*		
Borderline	4	12,4	3,1	4,986667		
Cystadenocarcinoma	8	601,6	75,2	5422,883		
Cystadenoma	12	120,3	10,025	303,573		
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	24018,25	2	12009,12	6,104199	0,008132	3,4668
Within Groups	41314,44	21	1967,354			
Total	65332,69	23				

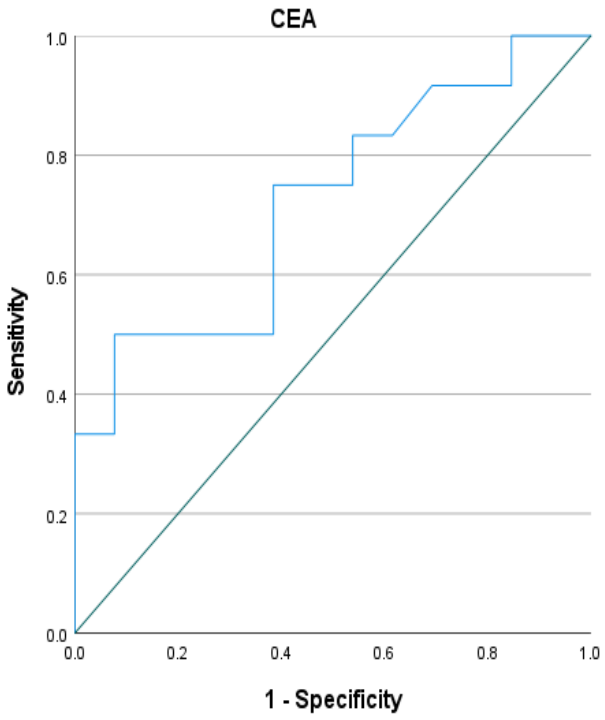


Figure 13 Sensitivity and specificity of tumour marker CEA in diagnosing mEOC.

The Receiver Operating curve (ROC) in figure 13 above was used to calculate the sensitivity and specificity of tumour marker CEA. The area under the curve (AUC) is 0.721(95% CI). This makes the tumour marker CEA an acceptable tool for the diagnosis of malignancy.

Tumour marker CA19-9

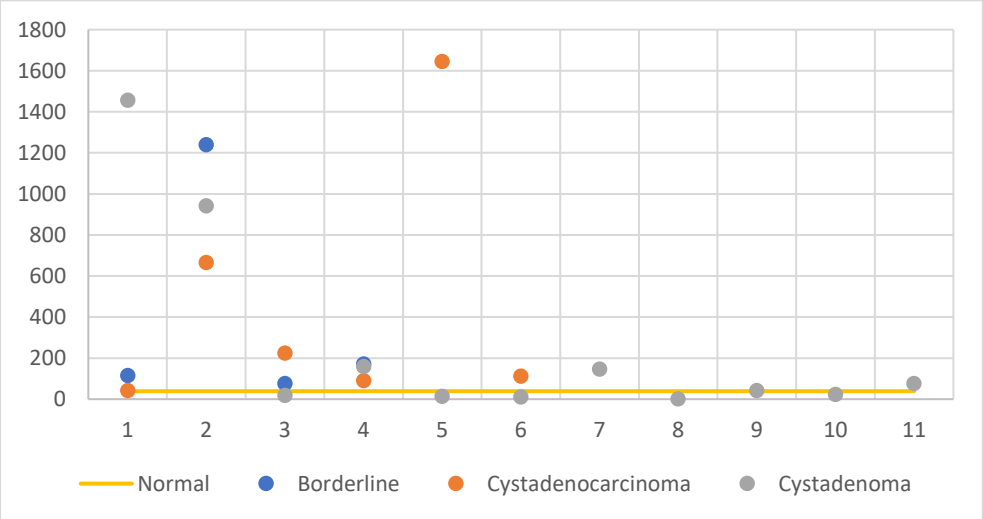


Figure 14 Tumour marker CA19-9

Figure 14 and table 12 show that the tumour marker CA19-9 levels for mucinous cystadenoma, mucinous borderline tumours and mucinous cystadenocarcinoma were all above the normal range which has also resulted in higher mean levels of 262,76 U/mL, 401,25 U/mL and 463,33 U/mL respectively. The p-value of 0,746 shows that these findings were not statistically significant.

Table 12 Analysis of variance of CA 19-9

Anova: Single Factor						
Groups	*Count*	*Sum*	*Average*	*Variance*		
Borderline	4	1605	401,25	314187,6		
Cystadenocarcinoma	6	2780	463,3333	386855,9		
Cystadenoma	11	2890,4	262,7636	230626,8		
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	171019,9	2	85509,96	0,296961	0,746644	3,554557
Within Groups	5183110	18	287950,5			
Total	5354130	20				

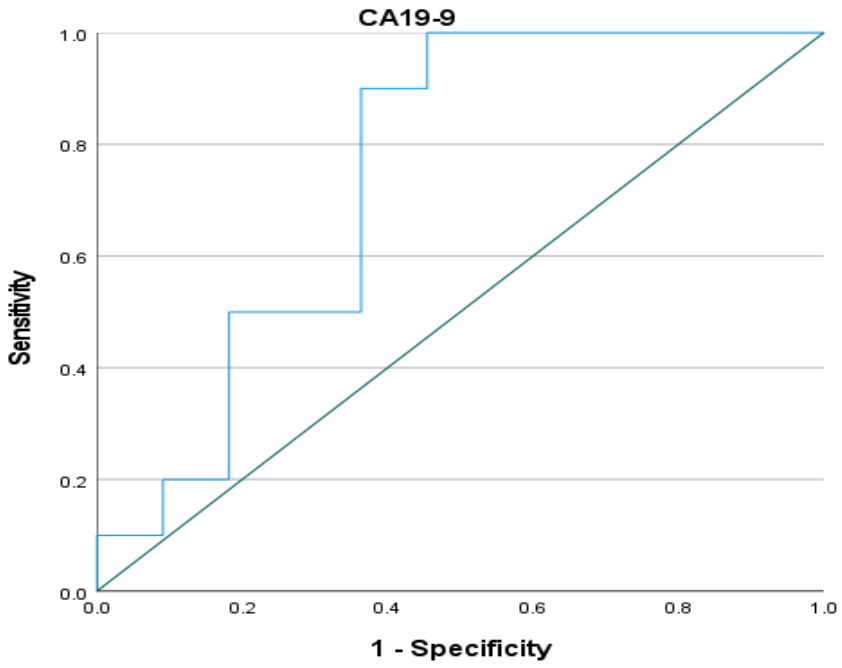


Figure 15 Sensitivity and specificity of tumour marker CA 19-9 in diagnosing mEOC

The Receiver Operating curve (ROC) of tumour marker CA 19-9 was used to calculate sensitivity and specificity for diagnosing mEOC. The area under the curve (AUC) is 0.745(95% CI). This makes the tumour marker CA 19-9 an acceptable tool for the diagnosis of malignancy.

4.3.8 Preoperative workup

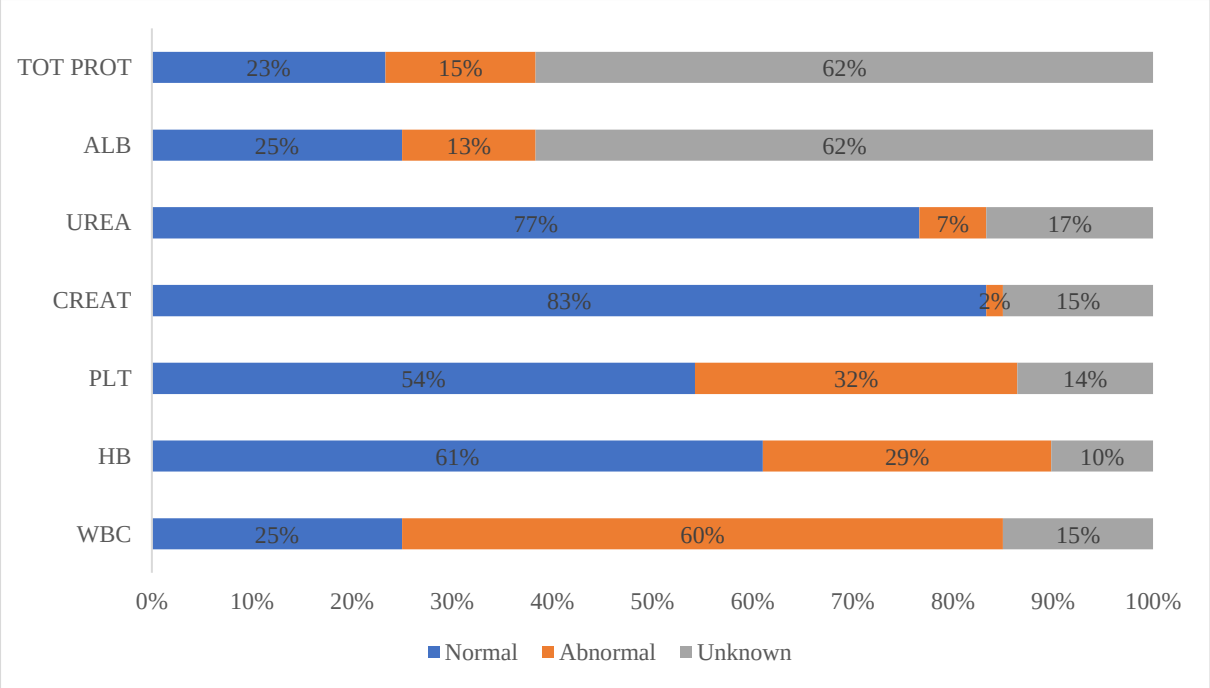


Figure 16 Preoperative work-up

Results show that most patients (60%) had abnormal white blood count (WBC). 29% of the patients had abnormal haemoglobin (HB), 32% of the patients had abnormal platelet (PLT), 13% of the patients had abnormal had abnormal albumin (ALB), and 15 % of the patients had abnormal total protein (TOT PROT). The majority of patients had a normal Urea (77%) and creatinine (83%).

Table 13 Preoperative descriptive statistics

Descriptive statistics	*WBC 10^9/L*	*HB g/dL*	*PLT 10^9/L*	*CREAT µmol/L*	*UREA mmol/L*	*ALB g/L*	*TOT PROT g/L*
Mean	8,21	12,21	386,82	72,00	4,43	36,09	72,57
Standard Error	0,41	0,33	23,62	5,06	0,20	1,60	1,95
Median	8,07	12,5	343	66	4,5	39	75
Mode	5,9	11	474	60	4,9	40	84
Standard Deviation	2,92	2,43	168,65	36,13	1,43	7,69	9,36
Range	13,34	12,5	1038	265	6,9	27	31
Minimum	2,5	3,6	168	36	2	19	54
Maximum	15,84	16,1	1206	301	8,9	46	85
Count	51	53	51	51	50	23	23
Confidence Level (95,0%)	0,822	12,88	47,435	10,161	0,407	3,326	4,048

On average, the pre-operative workup variables were normal with a mean of WBC of 8,21x10^9/L which falls within the normal range of 4-11x 10^9 /L; HB of 12,21g/dL(women normal range 11,5 – 16 g/dL) ; PLT of 386x10^9/L (normal range 150-400 x 10^9/L) ; CREAT of 72 µmol/L(normal range 70- 150 µmol/L); UREA of 4,43 mmol/L(normal range 2,4-6,7) ; ALB of 36,09 g/L(normal range 35-50 g/L) and finally TOT PROT of 72,57g/L(normal range 60-80). Although the PLT was on average normal, most patients had a mode of 474 which is on the abnormal side and implies that most patients had a higher PLT.

4.4 To describe the surgical outcomes of malignant mucinous ovarian tumours compared with benign mucinous tumours.

4.4.1 Treatment modalities

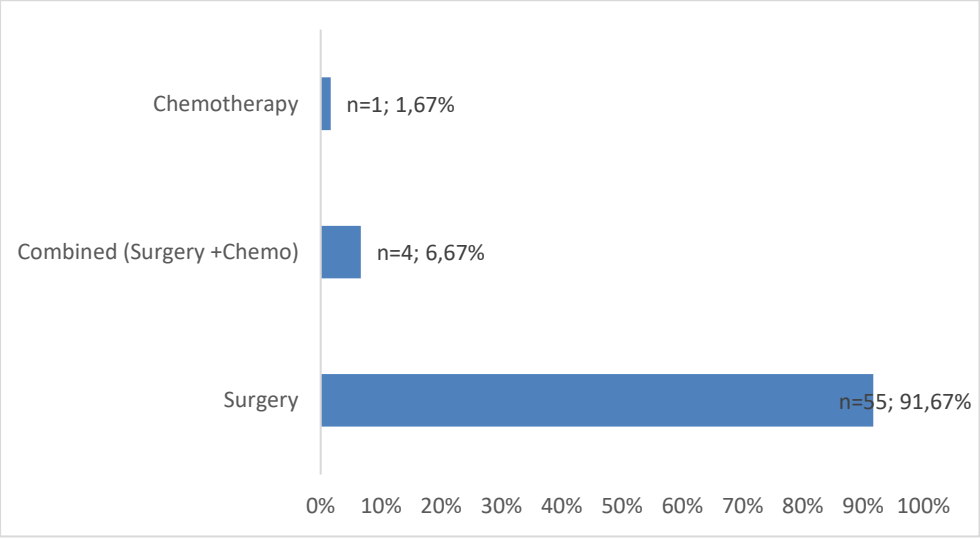


Figure 17 Treatment modalities

In this study three kinds of treatments were conducted i.e, surgery alone was conducted in 55 (91,67%) patients and of these patients, 10 were those diagnosed with mucinous cystadenocarcinoma; Combined surgery and adjuvant chemotherapy were done in 4(6,67%) patients and 1(1,67%) patient was treated with chemotherapy alone. Of the four patients treated with combined surgery and adjuvant chemotherapy 2 were ECOG PS 2(FIGO stage not indicated), 2 patients were ECOG PS 3(FIGO stage IV C) and 1 patient was ECOG PS 4(FIGO stage IV C).

As for comorbidities among the patients treated with combined surgery and chemotherapy, 1 patient had a history of previous myocardial infarction (MI) and percutaneous coronary intervention (PCI), 1 patient was schizophrenic and also had hypothyroidism. The remaining 2 patients did not have any other comorbidities.

Table 14 Treatment modalities by histology subtypes

	MUCINOUS BORDERLINE TUMOUR	MUCINOUS CYSTADENOMA	MUCINOUS CYSTADENOCARCINOMA	Total
Surgery	10	35	10	55
	16,67%	58,33%	16,67%	91,67%
Combined (Surgery +Chemo)	0	0	4	4
	0,00%	0,00%	6,67%	6,67%
Chemotherapy	0	0	1	1
	0,00%	0,00%	1,67%	1,67%
Total	10	35	15	60
	16,67%	58,33%	25,00%	
Pearson Chi-square: 16,3636, df=4, p=0,002569				

Table 14 shows that there is strong evidence of a significant association between treatment and histology subtype. (Chi-square: 16,363;df=4;p=0,002).

4.4.2 Intraoperative and postoperative complications

4.4.2.1 Surgery and surgical outcomes

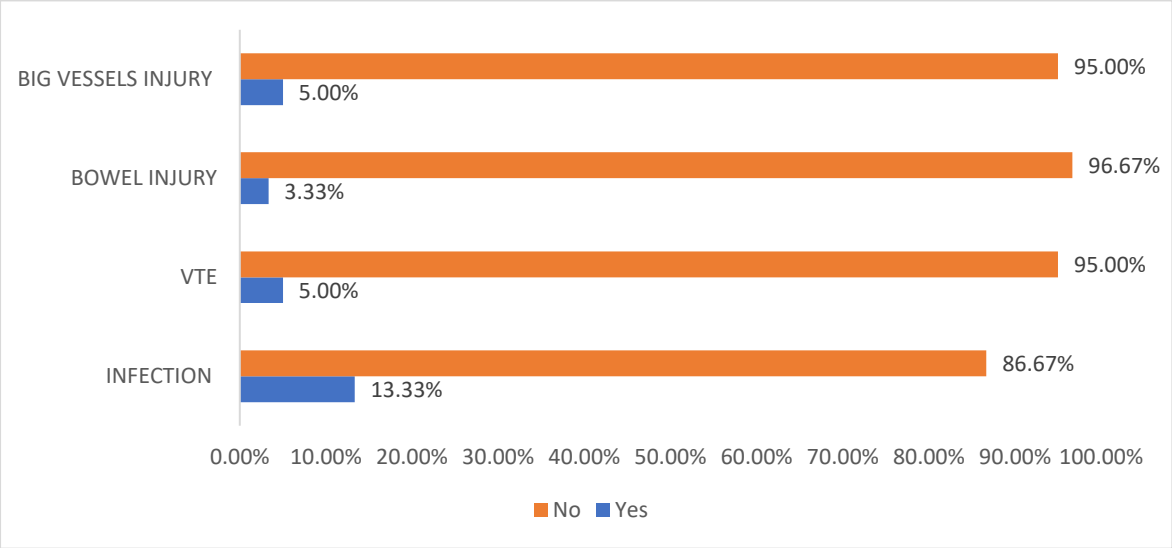


Figure 18 Intraoperative and postoperative complications

There were 3(5,00%) patients who had intraoperative complications and 13(21,67%) patients had postoperative complications. There were 8(13,33%) patients with post-operative infection, 3(5,00%) patients had a DVT, 3(5,00 %.) patients had a vascular injury and 2(3.33%) patients had a bowel injury. Of these results, the 15 patients diagnosed with mucinous cystadenocarcinoma had only one patient with infection, one patient with DVT and one patient with vascular injury while none had bowel injury. There was a significant association between VTE and histology subtype (Chi-square: 6,666;df=2; p=0,035).

4.4.2.2 Hospital stay

Table 15 Hospital stay in days

HOSPITAL STAY	
Mean	13,717
Standard Error	1,926
Median	8
Mode	7
Standard Deviation	14,918
Range	90
Minimum	4
Maximum	94
Count	60
Confidence Level (95,0%)	3,854

The mean stay in hospital from day of admission until discharge was 13,71 days (SD±14,91, CI 95%) Minimum days were 4 to a maximum of 94 days of hospital stay. Most patients stayed at the hospital for 7 days measured by mode. Hospital stays for patients diagnosed with mucinous cystadenocarcinoma was between 16 and 94 days.

4.4.2.3 Readmission

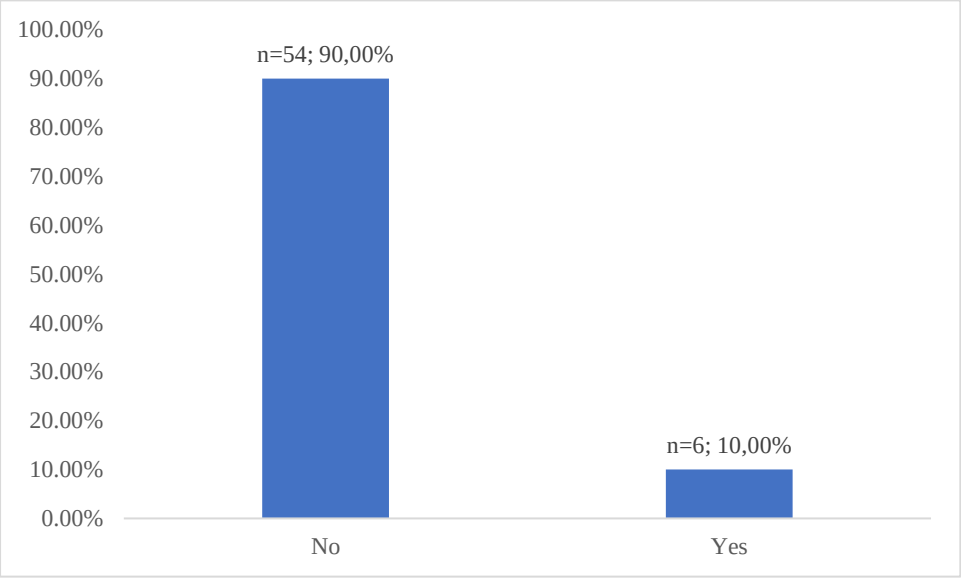


Figure 19 Readmission

Figure 19 shows that there were 6(10,00%) of patients who were readmitted to the hospital. The indications for readmission were postoperative infection in 5 of 6 patients, and bowel obstruction in 1 of 6 patients. Only 2 of 15 patients diagnosed with mucinous cystadenocarcinoma were readmitted while the other 13 patients were not.

4.5 Death and the survival estimates on patients with malignant lesions

Of the 7(11,67%) patients that died between the duration of study in the sample or population of 60 patients, 2(3,33%) patients died per year respectively in 2011, 2013 and 2017 while one patient died in 2014. None of the patients with cystadenoma died of the disease, 1(1,67%) patient with mucinous borderline tumour died 1 week following surgery secondary to big vessels injury and 6 (10,00%) patients with cystadenocarcinoma died of the disease.

The mean survival period from the date of surgery to death / last time seen was 20,5 months.

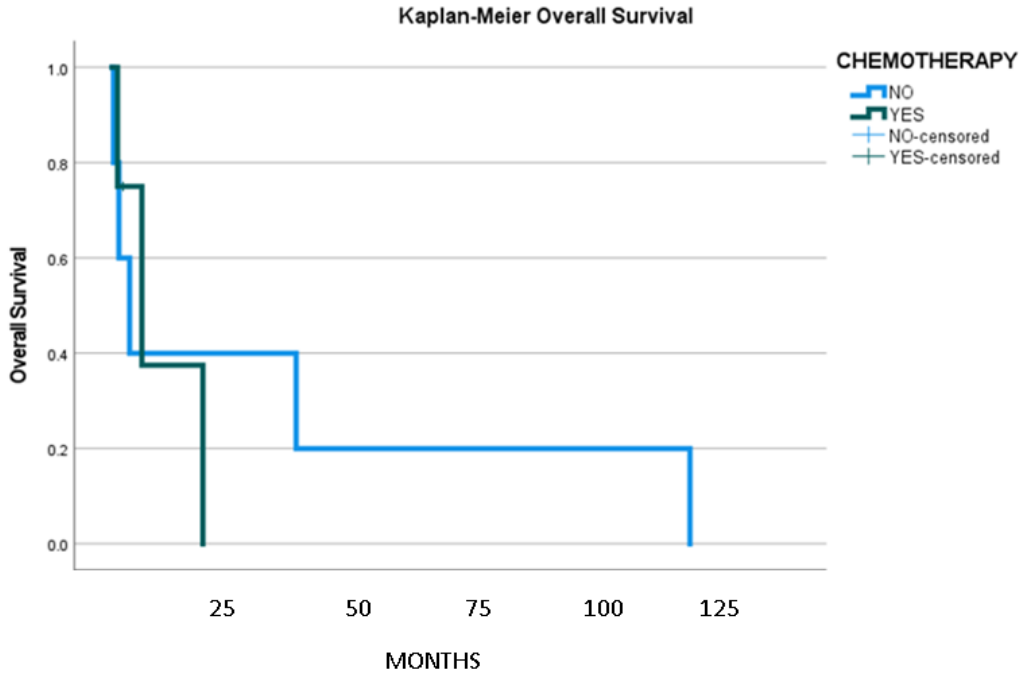


Figure 20 Survival estimates

Figure 4.20 shows the Kaplan Meier survival estimates comparing survival in women who underwent surgery alone and those who received chemotherapy after surgery.

The survival curve of patients with cystadenocarcinoma who were treated with both surgery and chemotherapy was compared to that of those treated with surgery alone. The median survival time was 8 months (95% CI) for patients treated with both surgery and chemotherapy and 12months (95%CI) for patients treated with surgery alone.

4.6 Conclusion

This Chapter presented the results of the study to ensure that objectives are met. The socio-demographic factors of patients with mucinous ovarian tumours were presented, clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours, the surgical outcome of malignant mucinous ovarian tumours compared with benign mucinous tumours and survival estimates on patients with malignant lesions were calculated.

CHAPTER 5: DISCUSSION OF RESULTS AND FINDINGS

5.1 Introduction

This chapter discusses the results and summarizes the findings according to the literature review and the results presented in the preceding chapter in line with the study objectives and research questions.

The objectives of the study were to:

1. To describe the socio-demographic factors of patients with mucinous ovarian tumours in general.
2. To describe the clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours.
3. To describe the surgical outcome of malignant mucinous ovarian tumours compared with benign mucinous tumours.
4. To calculate the survival estimates on patients with malignant lesions.

5.2 Discussion

5.2.1 The socio-demographic factors of patients with mucinous ovarian tumours in general.

The mean age of the study population was 49,95 years (SD±16,53) with a range of 13 years as a minimum to 80 years as the maximum age (95%CI, 45,67-54,22). The mean age of patients with mucinous cystadenoma was 49,06(SD±16,00) with a range of 13 years as minimum age to 76 years as the maximum (95%CI, 44,00-54,12). The mean age of patients with mucinous borderline tumours was 53,40±6.36 years with a range of 19 years as minimum age to 80 years as the maximum (95%CI, 48,18-58,62). The mean age of patients with mucinous adenocarcinoma was 49,73±4,15 years with a range of 18 years as minimum age to 78 years as the maximum (95%CI, 40,83-58,64). The p value was 0,761 and we conclude that this does not reach statistical significance. Morice and colleagues in their study reported a median age of 53 years when comparing mucinous ovarian carcinoma with high-grade serous ovarian cancer.[32]

Most patients were above the age of 50(53,40%) compared to 46,60% that were below the age of 50. Of those patients below the age of 50, 11(18,33%) patients were within the age

group of 30-40 years, 10(16,7%) patients were within the age of 40-50 years, 5(8,33%) patients were within the age group of 10-20 years of age and 2(3,33%) patients contributed to the age group of 10-20 years. This illustrates the need for fertility-sparing surgery in patients presenting with ovarian mucinous tumours. As said by Morice and colleagues in their study mucinous ovarian cancer is the most common histologic subtype in the subgroup of patients who are eligible for fertility-sparing surgery.[32] The risk of recurrence following fertility-sparing surgery for ovarian mucinous cancers is lower than that reported for women with stage I serous cancers (6% vs. 20%, P<0,001). For young patients wishing to preserve their fertility, a unilateral salpingo-oophorectomy is usually proposed, with peritoneal staging procedures (cytology, peritoneal biopsies, and omentectomy). In older patients, bilateral salpingo- oophorectomy is preferred.[50,51]

In our study, the mean age of patients diagnosed with mucinous cystadenocarcinoma was 49,73 (SD ± 16,08; 95% CI, 40,83-58,64). Mucinous cystadenocarcinoma is expected from 18 years of age to 78 years of age. This is similar to what is reported in the current literature. Massad and colleagues in their study on the clinical outcomes among women with mucinous adenocarcinoma of the ovary report a median age at presentation of 55 years for mucinous adenocarcinoma.[52] In a recent analysis of data from the Surveillance, Epidemiology, and End Results (SEER)cancer registry, 26% of mucinous ovarian cancers were diagnosed in women younger than 44 years.[53] Thus making the mucinous adenocarcinoma the most common histologic subtype in the subgroup of patients who are eligible for fertility-sparing surgery.[32]

Out of the 60 patients included in this study 52 (86,67%) patients were HIV negative, and 8(13,33%) patients were HIV positive on highly active antiretroviral therapy (HAART). There was no significant association between HIV status and the histology subtypes (Pearson Chi-square: 1,112, df=2, p=0,573). Andrew Grulich and colleagues found in a meta-analysis on the incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients that the rates of most of the common epithelial cancers were not increased in HIV positive patients. This corroborates our findings.[54]

There were 6 (10,00%) patients that had a positive family history of a family member affected by cancer. Of the six family members affected 3(5,00%) had ovarian cancer while 1 (1,67%) family member had colon cancer, endometrial cancer, and breast cancer respectively. The Chi-square value of the 60 patients had a p-value of 0,000 which is strong evidence to

suggest that there is an association between mucinous tumours and a family history of cancer. The main results for a network of case-control studies in Italy from the Collaborative Group on Epidemiological Studies of Ovarian Cancer summarised by La Vecchia show that there is a strong association of ovarian cancer risk with a family history of ovarian cancer (and a few selected other neoplasms, including colorectum and endometrium).[55] However, the association with a family history of breast and/or ovarian cancer appears to be restricted to non-mucinous cancers.[56] Risk factors for serous ovarian cancer include nulliparity, early menarche, late menopause, and germline BRCA1 or BRCA2 mutations, none of which are risk factors for mucinous ovarian cancer.[56]

5.2.2 The clinico-biochemical and pathological profile of patients with malignant mucinous ovarian tumours.

The leading complaint at presentation was abdominal pain with 53 (88,33%) patients which includes all the 15 patients diagnosed with mucinous cystadenocarcinoma; followed by abdominal mass(distension) with 47(78,33%) patients which includes 13 of 15 patients diagnosed with mucinous cystadenocarcinoma. followed by weight loss in 23(38,33%) patients. Ascites was only present in 18(30,00%) patients with 14 being the patients diagnosed with mucinous cystadenocarcinoma. It was expected that the increased volume from mucin and size of the tumour will present in this manner. Abdominal pain and abdominal volume have been reported to be the most frequent symptoms at presentation for patients with mucinous ovarian tumours.[69] Results show that between clinical presentation and histology types, there is a significant association (Chi-square: 38,956, df=2, p=0,000) with the bulk of patients with cystadenocarcinoma having all the 3 commonest symptoms at presentation. This can be explained by the fact that adenocarcinoma is a continuum of cystadenoma through borderline tumour thus symptoms may be more pronounced.

The Eastern Cooperative Oncology Group (ECOG) functional score in the cohort at presentation had 28(46,66%) patients in stage I, 21(35,00%) patients in stage II while stage IV was represented by 6(10,00%) of the patients. There were 4 (6,67%) patients representing stage III participants and 1(1,67%) patient representing stage 0. Of the 15 patients diagnosed with mucinous cystadenocarcinoma there was none in stage 0, 1 patient in stage I, 5 patients were in stage II, 4 patients were in stage III, and 5 patients were in stage IV. These results had a significant association between the histology type and the ECOG staging (Chi-square:

31,602, df=8, p=0,000). Of the 15 patients with adenocarcinoma 14 presented as ECOG Performance status (PS) stage II-IV (stage II being: ambulatory and capable of all self-care but unable to carry out any work activities; stage III being capable of only limited self-care, confined to bed or chair more than 50% of waking hours, and stage IV being completely disabled; cannot carry out any self-care; totally confined to bed or chair up and about more than 50% of waking hours otherwise translated) Performance status (PS) of a patient is the assessment of the level of function and capability of self-care. It plays a key role in treatment decisions and is an independent prognostic indicator for patients with advanced malignancy.[57] Patients with poor PS have a higher risk of chemotherapy toxicity and poor outcome.[58] PS assessment has been shown to correlate with survival in many cancer forms. For example, in a study of 3825 patients with metastatic colorectal cancer receiving 5-fluorouracil, ECOG PS of 0 and 1 was associated with a longer duration of survival compared to ECOG PS >1.[59] In the setting of non-small-cell lung cancer patients receiving first-line, doublet, platinum-based chemotherapy regimens patients with an ECOG PS of 2 had a significantly worse survival outcome than patients with an ECOG PS of 0 or 1. In fact, the survival rate at one year for a patient with an ECOG PS of 0 was twice that of an individual with an ECOG PS of 2 (40 versus 19%,).[60]

Many patients were assessed histologically as early stages of the disease. The FIGO staging on these patients showed that 50(83,33%) patients were stage I, 8(13,33%) patients were stage IV, and 2(3,33%) patients were stage II. Of the 15 patients diagnosed with mucinous cystadenocarcinoma, the majority were in FIGO stage IV affecting 8 patients while 5 of 15 patients were in stage I, and 2 patients were in FIGO stage II. (Chi-square: 55,232, df=10, p=0,000). Our findings of early-stage tumours by FIGO staging at the time of diagnosis was in keeping with available literature that reports that mucinous neoplasms generally occur in young women and are diagnosed at an early stage, with 83% being diagnosed at stage I and only 17% at stage II or higher.[18] A potential explanation for this is that mucinous ovarian cancers are usually very large primary tumours (typically >15 cm in diameter) that generate symptoms while the disease is still localized to the ovary.

The subtype common to most of the participants was mucinous cystadenoma in 35(58,33%) patients, followed by mucinous cystadenocarcinoma in 15(25,00%) patients then mucinous borderline tumours in 10(16,67%) patients with 4(6,67%) being associated with Brenner

tumours. The current literature reports that approximately 80% of primary ovarian mucinous neoplasms are cystadenomas, approximately 5% of mucinous cystadenomas are associated with a dermoid cyst or a Brenner tumour, and approximately 10% of Brenner tumours are associated with a mucinous cystadenoma.[7] Kikkawa and colleagues in their study on mucinous ovarian tumours reported 99(24,75%)patients with benign mucinous ovarian tumours , 142(35,50%) patients with mucinous borderline tumour, and 159(39,75%) patients with cystadenocarcinoma.[61] Our malignancy rate is low (25,00%) compared to a documented literature of 39,75% in the above-named study. However, this is a very old study and since then the prevalence has been reviewed down. In fact, MOC was believed to constitute around 12% of ovarian malignancies. However, recent estimations show the true incidence to be at around 3%.[10] The two main reasons for this drop in incidence are the identification criteria, which separate benign mucinous tumours from invasive mucinous carcinoma, and better recognition of clinical and pathological features to differentiate between primary mucinous carcinoma and metastatic carcinoma of the ovary.[30] A more recent study done by Prat and colleagues found that benign mucinous neoplasms (cystadenoma and adenofibroma) accounted for 80% of cases. Mucinous borderline tumours were the next most common type, accounting for 16%-17% of cases. The remaining 3%-4% of primary tumours were ovarian mucinous carcinoma. These findings were different from our study findings and perhaps this was due to geographic variations.[62]

The chronic medical comorbidities were hypertension in 26(43,33%) patients, dyslipidaemia in 5(8,33%) patients; myocardial infarction in 4(6,67%) patients, hypothyroidism in 2(3,33%)patients; and cardiac arrhythmia in 1(1,67%)patients. This was expected in this study population with a mean age of 49,95 years.

Tumour markers levels were 127,90 U/mL (SD±291,97>35U/mL) for CA125, 29,87 ng/mL (SD±52,30>5 ng/mL) for CEA and 346,45 U/mL (SD±517,40>39 U/mL) for CA19-9.

The tumour marker CA 125 mean values were 59,94 U/mL for cystadenoma, 81,65 U/mL for mucinous borderline tumours and 289,04 U/mL for cystadenocarcinoma. There was a positive correlation of 48% between the marker levels and degree of malignancy with a consistent upward trend from benign (mucinous cystadenoma) through mucinous borderline tumours to malignancy (mucinous cystadenocarcinoma). Results also show that the variance between benign and malignancy did not vary significantly over time (p=0,090). The receiver

operating curve (ROC) of tumour marker CA 125 was used to calculate sensitivity and specificity for diagnosing mEOC. The area under the curve (AUC) was 0,742. This makes the tumour marker CA125 an acceptable tool for the diagnosis of malignancy.

The tumour marker CEA values had a significant difference between benign tumours (cystadenoma and mucinous borderline tumours); however, cancer (cystadenocarcinoma) showed remarkably high levels of CEA (p=0,008). CEA mean values of 3,10 ng/mL for mucinous borderline tumours was normal compared to 10,21 ng/mL for cystadenoma, and 75,2 ng/mL for cystadenocarcinoma which were above the normal range. The variance between benign and malignancy did vary significantly over time with a p-value of 0,008. The area under the ROC curve (AUC) was 0,721. This makes the tumour marker CEA an acceptable tool for the diagnosis of malignancy. As with mucin-producing gastrointestinal tumours, serum CEA is typically elevated in mucinous ovarian carcinomas. While 19% of non-mucinous ovarian cancers may exhibit elevated CEA levels, 88% of MOCs will display an elevated CEA. However, MOCs will also produce CA-125 (100% in one report), so an elevated serum CA-125 does not exclude mucinous histology. Santoribio and colleagues examined 94 patients with mucinous cystadenomas, mucinous borderline tumours, or MOCs and found that elevations in CA19-9 and CA-125 were most helpful in predicting malignancy, while CEA and CA 15-3 were less sensitive.[63] Wei Lin and colleagues in a retrospective cohort study on the prognostic significance of preoperative serum CEA in primary mucinous ovarian carcinoma found that the preoperative serum CEA was elevated (>5,0 ng/mL) in 10 patients (17,5%), with a median serum CEA of 9,6 ng/mL (5,4–111,7 ng/mL). CEA was significantly associated with preoperative serum cancer antigen 125 (*P*=0,002), and tumour stage (*P*=0,001). Univariate analysis showed that patients with elevated CEA had significantly worse overall survival (OS) than patients with normal CEA (5-year OS: 50,8% vs 91,9%, respectively; *P*=0,013), but there was no significant difference in progression-free survival between the two groups (*P*=0,307).[64]

The tumour marker CA19-9 values for all the 3 histological subtypes were all above the normal level which has also resulted in higher mean levels of 262,76 U/mL for mucinous cystadenoma, 401,25 U/mL for mucinous borderline tumours, and 463,33 U/mL for mucinous cystadenocarcinoma. The p-value was 0,740 showing that these values did not vary. The ROC area under the curve (AUC) was 0,745. This makes the tumour marker CEA an acceptable tool for the diagnosis of malignancy. Superior discrimination.[70] Santotoribio and colleagues examined 94 patients with mucinous cystadenomas, mucinous borderline

tumours, or MOCs and found that elevations in CA19-9 and CA-125 were most helpful in predicting malignancy, while CEA and CA 15-3 were less sensitive.[63]

On average, the pre-operative workup variables were normal with a mean of WBC of 8,21x10^9/L(normal range 4-11x 10^9 /L); HB of 12,21g/dL (women normal range 11,5 – 16 g/dL); PLT of 386x10^9/L (normal range 150-400 x 10^9/L) ; CREAT of 72 μmol/L(normal range 70- 150 μmol/L); UREA of 4,43 mmol/L(normal range 2,4-6,7) ; ALB of 36,09 g/L(normal range 35-50 g/L) and finally TOT PROT of 72,57g/L(normal range 60-80). Although the PLT was on average normal, most patients had a mode of 474 which is on the abnormal side and implies that most patients had a higher PLT.

5.2.3 The surgical outcome of malignant mucinous ovarian tumours compared with benign mucinous tumours

In this study three kinds of treatments were conducted. i.e., surgery alone was conducted in 55(91,67%) patients and of these patients, 10 had mucinous cystadenocarcinoma; combined surgery and adjuvant chemotherapy were done in 4(6,67%) patients and 1(1,67%) patient was treated with chemotherapy alone. Of all the 15 women with cystadenocarcinoma, only 5(33,33%) patients received chemotherapy. Two patients with adenocarcinoma who qualified for chemotherapy did not receive chemotherapy because they died two days after the surgery due to complications of other comorbidities. And the remaining patients were FIGO stage 1 hence not given chemotherapy as per our oncology protocols. Surgery remains the mainstay of treatment for early-stage disease. Surgery is often curative for patients with early-stage disease (International Federation of Gynaecologic Oncology (FIGO) stage I). For the small subset of patients with early-stage disease who require adjuvant treatment, the recommended regimen remains controversial. Compared to the more common high grade serous ovarian carcinomas, MOCs have lower response rates to the traditional carboplatin/taxane-based regimen and have worse stage-specific outcomes.[43,2]

Of the four patients treated with combined surgery and adjuvant chemotherapy 2 were ECOG PS 2(FIGO stage not indicated), 2 patients were ECOG PS 3(FIGO stage IV C) and 1 patient was ECOG PS 4(FIGO stage IV C).

As for comorbidities among the patients treated with combined surgery and chemotherapy, 1 patient had a history of previous myocardial infarction (MI) and percutaneous coronary

intervention (PCI), 1 patient was schizophrenic and had hypothyroidism. The remaining 2 patients did not have any other comorbidities. The advanced stage at the time of presentation combined with comorbidities could explain why patients with adenocarcinoma treated with both surgery and chemotherapy had slightly worse outcomes compared with those treated with surgery alone.

The commonest complication was infection in 8(13,33%) patients, venous thromboembolic event and big vessels injury in 3(5,00%) patients each followed by bowel injury in 2(3,33%) patients. Of these results, the 15 patients diagnosed with mucinous cystadenocarcinoma had only one patient with infection, one with VTE and one with big vessel injury while none had bowel injury. There was a significant association between VTE and histology subtype (Chi-square: 6,666, df=2, p=0,035). Benedetti and colleagues, in one study in patients with advanced ovarian cancer undergoing primary cytoreductive surgery, reported early postoperative complications (defined as complications occurring within 30 days after surgery) as follows: 39(32,30%) pulmonary (pleural effusion and pneumonitis), 11(9,10%) infective, 5(4,20%) cardiovascular,4(3,30%) gastrointestinal and 3(2,50%) haematological.[68] The distribution of complications in our study is different. Wound infection and thromboembolic events as the leading causes of complication in our study may be explained by obesity and resultant poor wound care and low socio-economic level of our study population.

The mean stay in hospital from day of admission until discharge was 13,71 days (SD±14,91, CI 95%). Minimum days were 4 to a maximum of 94 days of hospital stay. Most patients stayed at the hospital for 7 days measured by mode. Hospital stays for patients diagnosed with mucinous cystadenocarcinoma was between 16 and 94 days. Our findings are in keeping with what Benedetti and colleagues have found in a study of patients with advanced ovarian cancer undergoing primary cytoreductive (a mean length of hospitalisation of 7 days with a range from 4 to 22 days).[65]

Six patients 6(10,00%) were readmitted to the hospital following surgery and discharge from the hospital. Reasons for readmission range from infection indicated in 5 of 6 patients while readmission due to bowel obstruction was indicated in one of 6 patients. Only 2 of 15 patients diagnosed with mucinous cystadenocarcinoma were readmitted while 13 did not. This illustrates once again that wound infection is the leading cause of complication in our study

possibly explained by obesity and resultant poor wound care and low socio-economic level of our study population.

5.2.4 The survival estimates on patients with malignant lesions

Of the 7(11,67%) patients that died between the duration of study in the population of 60 patients, none of the patients with cystadenoma died of the disease, 1(1,67%) patient with borderline mucinous tumour died 1 week following surgery secondary to big vessels injury and 6 (10,00%) patients with cystadenocarcinoma died of the disease. None of the patients with cystadenoma died of the disease and this was expected as the survival is documented to be good for women with mucinous ovarian cancer diagnosed at an early stage. Sixty-five to 80% of mucinous ovarian cancers are diagnosed at an early stage. Thus, the overall prognosis is much better for women with mucinous ovarian cancer than for those with other subtypes of epithelial ovarian cancer. Five-year overall survival among patients with mucinous ovarian cancer confined to the ovary exceeds 90%.[32]

The mean survival period from the date of surgery to death / last time seen was 20,5 months. The median survival time was 8 months for patients treated with both surgery and chemotherapy and 12months for patients treated with surgery alone. As reported in the literature, the five-year overall survival among patients with mucinous ovarian cancer confined to the ovary exceeds 90%; by contrast, when mucinous ovarian cancer has spread to the peritoneum in the abdominal cavity or beyond (stage III or IV), the estimated median overall survival is between 12 and 33 months.[53,2,66] In other 4 different studies, the OS after platinum-based therapy were as follows:33,2 months; 21,6 months; 14 months and 35 months respectively.[66,43,67,68] A Swedish registry study with over 6000 women with ovarian cancer demonstrated that women with mucinous histology had improved overall survival compared to women with serous subtypes (70 versus 34months), most certainly owing to an earlier stage at diagnosis.[71] In the GCIG trials[11], Mackay and colleagues demonstrated that for patients with FIGO stage III and IV disease, the prognosis for the 3% of cancers classified as mucinous was substantially worse than for serous carcinomas with the median overall survival (OS) of 14,6 months compared with 40,8 months. Data from Mackay and colleagues and from six smaller similar studies reaching the same conclusions have also been summarized by Naik and colleagues.[22]

The median survival time for cystadenocarcinoma on patients who were treated with both surgery and chemotherapy as well as those treated with surgery alone was low compared to reports from literature (30,18 weeks (95%CI)) and 48,9 weeks (95%CI) respectively. This was way less than what was reported by Kikkawa and colleagues in a similar study (10-year survival rate of 7,7% in patients with carcinoma.[61] In our setting, this can probably be explained by the late presentation to the gynaecological oncology clinic. Patients with unspecific symptoms (which is frequent in ovarian malignancy) waste valuable time at lower-level facilities where highly trained personnel and quality imaging (ultrasound and CT scan) are not readily available. However, this was also a small study, and its findings cannot be used to give a conclusive association.

5.3 Summary

Mucinous ovarian tumours can affect all extremes of ages. A quarter of mucinous ovarian tumours is likely to be malignant. There is no significant association between HIV status and the histology subtypes. There was a strong association between mucinous tumours and a positive family history of cancer. The leading complaint at the time of presentation was abdominal pain. Most patients with mucinous ovarian tumours presented at an early stage (FIGO stage I). Mucinous cystadenoma was the commonest subtype found. Mucinous cystadenomas and mucinous borderline ovarian tumours have excellent surgical outcomes compared to mucinous cystadenocarcinomas. The tumour marker CA-19-9 was more sensitive than CA 125 in predicting ovarian mucinous cancer. The mean survival period (from the date of surgery to death / last time seen) for mEOC has remained at around 1-year whether adjuvant chemotherapy was given or not.

CHAPTER 6: CONCLUSION

Ovarian mucinous tumours have remained a gynaecological condition affecting a good part of women in the reproductive age and have a good prognostic of cure with an early presentation, thus fertility sparing surgery/treatment should be discussed and consider in all women in this age group having fertility desires.

Abdominal pain and distension in women of all age groups should raise awareness for mucinous ovarian tumours. Clinicians should have a high index of suspicion as these two symptoms are the leading complaints in patients with ovarian mucinous tumours.

Most patients with mucinous ovarian tumours are diagnosed at an early stage and do not need adjuvant therapy, being cured by surgery alone. The regimen and the benefit of adjuvant chemotherapy for advanced mEOC is yet to be proved and defined. As platinum-based chemotherapy does not significantly improve the survival time complete resection of mucinous tumours is particularly important to achieve a good prognosis.

Because of the low accrual of this tumour, many of the conclusions about malignant mucinous tumours of the ovary have been based on relatively few cases in each subcategory and have included cases in which staging or microscopic sampling or both have been suboptimal. Uncertainties associated with these tumours can be satisfactory reduced or eliminate only with detailed future investigations.

CHAPTER 7: RECOMMENDATIONS

Registrars and all the clinical staff are encouraged to keep more accurate records as this does not only serve to improve the patient management and outcomes but also helps with academic research thus progress in medicine.

There is a need for funded international trials or large multicentre prospective studies to be done and to consider the slow accrual of these tumours.

CHAPTER 8: LIMITATIONS OF THE STUDY

This was a retrospective study based on the patients' records (files). A lot of information was missing to an extent that it was unknown whether the women who were followed up until "last seen'' were still alive.

Problems in the differential diagnosis of primary and metastatic mucinous ovarian tumours made some patients have had their primary surgery at General Surgery Department then referred to the Gynaecology Oncology Unit at a later stage. On the other hand, some women were operated at the Gynaecological Oncology Unit first then referred to the Department of Surgery as it was found that the primary site was not gynaecological.

The study was beset by inadequate surgical staging and pathological sampling. Some patients had several files under different hospital numbers, with different histology results e.g., mucinous borderline in one file and pseudomyxoma peritonei in another file.

Although it is acknowledged that cystadenocarcinoma is a rare tumour, over a period of ten years, we only had sixty mucinous ovarian tumours of which only fifteen were cystadenocarcinomas.

CHAPTER 9: STRENGTH OF THE STUDY

The strength of the study is that it was extended over the period of 10 years and we were able to directly access the patient files, theatre notes and all the laboratory results through NHLS.

CHAPTER 10: REFERENCES

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LIST OF ANNEXURES

Annexure 1: Data collection sheet

Demographics at Time of Diagnosis

Age						
Date of presentation						
Date of admission						
Date of surgery						
HIV	yes	no	ARVs		Unknown	
	Type of ARVs					
Contraception	None	O and P		P only	Others	
Family history of cancer	Ovary		Breast		Lynch	

Modality of Diagnosis

Date of diagnosis				
Method of diagnosis	TAH/BSO	Cystectomy	Laparoscope	Biopsy
Histological subtype				

Clinical Presentation

Abdominal pain	
Anorexia	
Weight loss	
Abdominal mass	
Abnormal uterine bleeding	
Postmenopausal bleeding	
PV discharge	
GI complaints with ascites	
PR bleeding	
Asymptomatic	

Stage at Presentation

ECOG	0	1	2	3	4	Unknown

FIGO STAGING		
IA		
IB		
IC	IC1	
	IC2	
	IC3	
IIA		

IIB		
IIIA	IIIA1	
	IIIA2	
IIIB		
IVA		
IVB		

Treatment Modalities

Treatment	Surgery	Surgery plus Chemo	Chemotherapy
Pathology report			

Appendix

Normal	Abnormal	Unknown
Appendectomy	Done	None

Histology	Malignant	Benign	Unknown

Post-Op Complications

Hospitalization stay	Days	

Clexane	Yes	No
Complications:		

Infection		
Bleeding	Vagina	
	Abdomen/Pelvis	
Damage to nearby organs	Bowels	
	Bladder	
	Ureters	
	Other organs	
Thromboembolic event		
Lymphedema		

Discharge and Follow Up Post Surgery

week	4	6	8
Findings	Recurrence	Ascites	Weight gain

Follow Up Management

Chemotherapy	No chemotherapy

Follow up	Yes	No

Work Up

ECG	Normal	Abnormal	Unknown
Ultrasound	Normal	Abnormal	Unknown
CXR	Normal	Abnormal	Unknown
CT- abdomen/Pelvis			

	Normal range	Value	Unknown
CA 125	0-35 u/ml		
α-FP	<10ng/ml		
β hCG	<15ng/ml		
LDH	48-115IU/L		
HE4	≤ 150 pM//L		

CEA	3ng/mL		

Comorbidities

Diabetes	Yes	No	Treatment	Yes	No	Controlled	Yes	No	
hypertension	Yes	No	Treatment	Yes	No	Controlled	Yes	No	
COPD	Yes	No	Treatment	Yes	No	Controlled	Yes	No	
TB	Yes	No	Treatment	Yes	No	Controlled	Yes	No	
Dyslipidaemia	Yes	No	Treatment	Yes	No	Controlled	Yes	No	
Other	Yes	No	Treatment	Yes	No	Controlled	Yes	No	

Preoperative Workup

White Cell Count		Haemoglobin		Albumin	

Annexure 2: WHREC Clearance Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr EK Ndala
School of Clinical Medicine
Department of Obstetrics and Gynaecology
Charlotte Maxeke Johannesburg Academic Hospital

E-mail: ellyndala@yahoo.com

CC: Supervisor: Dr L Mbodi <mlangi2005@yahoo.co.uk>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/01/23

REF: *R14/49*

PROTOCOL NO: **M1911117** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Clinical characteristics and outcomes: 10-year review of mucinous ovarian tumors at Charlotte Maxeke Johannesburg Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Annexure 3: Permission letter from Office of the Hospital CEO, CMJAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email: Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
10 October 2019

Dear Dr. E. Ndala

STUDY TITLE: Clinical Characteristics and Outcomes: 10-Year Review of Mucinous Ovarian Tumours At Charlotte Maxeke Johannesburg Academic Hospital.

Permission to review patient file for conduction of the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 18/10/2019

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 11.10.2019

Annexure 4: Permission Letter from the Department of Anatomical Pathology/NHLS/AAR

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

NATIONAL HEALTH LABORATORY SERVICE

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Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail : Yvonne.perner@nh;s.ac.za

Dr Y Perner MBBCh (Witwatersrand) FCPath (SA); MMed (Witwatersrand)

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

December 18, 2019

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr KE Ndala with his research entitled "Clinical characteristics and outcomes: 10 years of review of mucinous ovarian tumours at Charlotte Maxeke Johannesburg Academic Hospital".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Ndala will be in contact with the Department of Anatomical Pathology in respect of this.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

Annexure 5: Permission Letter from Head of Department, Obstetrics and Gynaecology

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Office of the Head of Department: Obstetrics and Gynaecology
Enquiries: Prof. L. Chauke

Tel: 011 488-3179
Fax:011 643-2522

08 October 2019

Ms G. Bogoshi
CEO
Charlotte Maxeke Johannesburg Academic Hospital
Parktown
Johannesburg

Dear CEO

Re: Request to conduct research titled:

Permission to obtain: Clinical Characteristics and outcomes: 10-Years review of Mucinous Ovarian Tumours at Charlotte Maxeke Johannesburg Academic Hospital: - Dr K E Ndala.

The above matter refers. I have looked at the protocol and **satisfied to recommend** that he be granted permission to conduct the study as proposed. The candidate has also satisfied the requirements of the Wits Human Research Committee.

Thank you

Dr H. Rhemtula
Principal Specialist and Acting Head
Department of Obstetrics and Gynaecology
Charlotte Maxeke Johannesburg Hospital and the University of the Witwatersrand

Annexure 6: NHLS Academic Affairs and Research Permission Letter

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

24 August 2020

Applicant: Kambola Elie Ndala
Institution: University of the Witwatersrand
Department: Obstetrics and Gynaecology
Email: ellyndala@yahoo.com
Tel: 011 488 3176 **Cell:** 078 364 2939

CC: Yvonne Perner
HOD – Anatomical Pathology (NHLS)

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project **"Clinical characteristics and outcomes: 10-year review of mucinous ovarian tumors at Charlotte Maxeke Johannesburg Academic Hospital"** using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***as per the attached patient list*** to conduct the proposed study as outlined in the submitted application. Submissions should be made annually on the AARMS system – https://aarms.nhls.ac.za.

Please note that approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.
- All data requested should be in accordance with the research protocol submitted and approved by the relevant Ethics Committee.
- Request for the inclusion of the NHLS as a source of data in the original protocol to be approved by Ethics as NHLS does not have a Human Research Ethics Committee.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

NATIONAL HEALTH LABORATORY SERVICE HELPDESK
Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk6@nhls.ac.za

ACCESS TO DATA FROM CDW FMI0069

Each application will be approved or rejected subject to the ability to extract this data and the availability of the data, and subject to the intended usage of the requested data. Applications that are incomplete and/or do not contain supporting documentation, will be rejected.

APPLICANT DETAILS			
Applicant's Name and Surname	Kambola Elie Ndala	**Title**	Dr
Telephone Number	(011)4883176	**Cell Phone Number**	(+27)783642939
Email Address	ellyndala@yahoo.com		
Business Role / Designation	Registrar, Medical University of Witwatersrand	**Name of Laboratory/ Department/ External Organisation**	O&G Department
Supervisor / Manager Name and Surname	Langanani Mbodi	**Telephone Number**	(082 7574072
Supervisor / Manager Designation	Specialist Consultant Gynaecological Oncologist	**Email Address**	mlangi2005@yahoo.co.uk

TERMS AND CONDITIONS

- Data / Information is not to be used in contravention of Sections 14, 15, 16 and 17 of the National Health Act 61 of 2004 and the Promotions of Access to information Act 2 of 2000 and the Protection of Personal Information (POPI) Act, 2013.
- The applicant undertakes to ensure that the data supplied to it by the NHLS is used ethically and solely for the purposes for which it is provided as detailed in this application, and further acknowledges that it shall remain liable for any breaches of this clause by the end user.
- If the purpose for the data requested in this application is for research, ethics approval and the full protocol must be attached to this application form. It is the responsibility of the applicant to obtain Ethics clearance from their regional human research ethics committee. to access the requested NHLS data.
- The applicant undertakes to store the NHLS data in a confidential manner by separating patient identifying details from laboratory data and storing the master list that links patient identifying details to study patient identifiers in a separate, secure location
- The applicant undertakes to provide the Academic Affairs and Research office at the NHLS with a copy of any report, presentation or publication emanating from the use of this data, if for research purposes.

ACCEPTANCE OF CONDITIONS

By signing this document the requestor and supervisor / Manager accept the terms and conditions as stated above.

Applicant Signature	Ndala	**Date**	16 /1 /2020
Supervisor / Manager Signature		**Date**	16 /1 /2020

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Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk6@nhls.ac.za

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Note: All fields in this section must be completed

DATA REQUEST DETAILS					
☑ Research Request ☐ Non- Research Request					
Request Type (Tick)	☑ New ☐ Modify / amend (Provide previous request details)	**Data Format (Tick)**	☑ Excel ☐ CSV	**Data Delivery (Tick)**	☐ CD / DVD ☑ Email ☐ Data link to specific table
Frequency of Extract (Tick)	☑ Once ☐ Repeat	**If Repeat, specify frequency (Tick)**	☐ Daily ☐ Weekly	☐ Monthly ☐ Annually ☐ Other	

DESCRIPTION OF REQUIRED DATA EXTRACT	
Overview of Data required	1) T-87000 (Ovary) M-84700 (Mucinous cystadenoma) 2) T-87000 (Ovary) M-84723 (Cystadenoma-borderline mucinous) 3) T-87000 (Ovary) M-84703 (Mucinous cystadenocarcinoma)
Region (For data extract, e.g. Province, Laboratory or Facility etc.)	Gauteng, Charlotte Maxeke Johannesburg Academic, Anatomical Pathology
Date range of extract (Period for which data is required)	01/01/2008 to 31/12/2017
Fields required (e.g. Test code or method, Episode number, etc.)	Episode/TJA number, patient name, hospital number, age, gender, date of birth

ADDITIONAL INFORMATION
Please cc fadila.ebrahim@nhls.ac.za in all correspondence regarding further requirements or for clarity on data required.

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DESCRIPTION OF INTENDED USE OF DATA EXTRACT
(e.g. research, epidemiology study, cost analysis of service, drug effectiveness, disease surveillance

MMED research

LIST WHO WILL HAVE ACCESS TO THIS DATA

Principal investigator: Dr. Ndala
Supervisor: Dr. Mbadi

PROJECT NAME AND REGISTRATION NUMBER
(If data is required for a registered research project. Please attach the Ethics Approval and full Protocol.)

Clinical characteristics and outcomes: 10 year review of mucinous ovarian tumors at CMJAH.
R14/49 Dr EK Ndala
Clearance certificate: M1911117

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NHLS RESPONSIBILITIES
The NHLS will: • **Ascertain if it is possible to extract the required data.** • **Register the application and issue a registration number.** • **Only release the requested data to the applicant whose name is specified on this application form.**
After this application has been completed and approved, please raise a service request with the NHLS IT Service Desk (Contact Number: (011) 386-6125/6/7/9): • **Send an email to helpdesk6@nhls.ac.za,** • **Scan this application form and attach it to the email, or fax it to (011) 386-6308.**

FOR OFFICE USE					
APPROVAL BY RESEARCH OFFICE (Research data requests only)					
Check List	☐ Data Request signed by Supervisor ☐ Ethics Approval attached ☐ Research Protocol attached				
Recommended / Reviewed by: **Manager - Academic Affairs and Research**	Dr Bakaty Malope-Kgokong	**Signature**		**Date**	24/08/2020
Approved by: **Executive Manager: Academic Affairs, Research and Quality Assurance**	Prof Koleka Mlisana	**Signature**		**Date**	01/09/2020
Endorsed by: **Chief Executive Officer**	Dr KS Chetty	**Signature**		**Date**	09/09/2020
Actioned by: **CDW Manager**		**Signature**		**Date**	/ /20
APPROVAL BY CDW (Non research requests only)					
Approved by: **CDW Manager**		**Signature**		**Date**	/ /20

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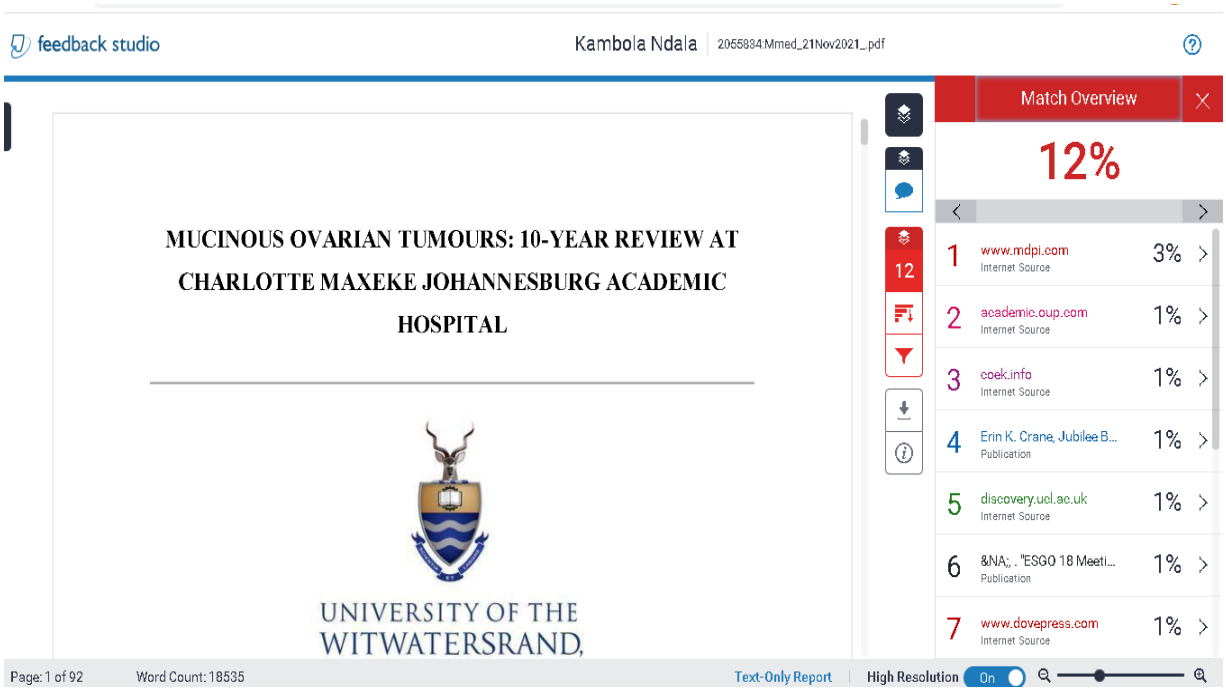
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