A COMPARISON OF MALIGNANT HISTOPATHOLOGICAL DIAGNOSES ON UTERINE CURETTINGS AND HYSTERECTOMY SPECIMENS

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A research report in 'submissible format' submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine (MMed) in the specialty of Anatomical Pathology.

Johannesburg, 2022

DECLARATION

Declaration: Students contribution to the article and agreement of co-authors

I, Abdullah Ismail, student number 0700203V, declare that this research report is my own work and I contributed adequately to the findings in the article submitted. It is being submitted in fulfilment of the requirement for the degree of Master of Medicine in the branch of Anatomical Pathology at the University of the Witwatersrand, Johannesburg. Assistance received has been acknowledged in the article. This work has not been submitted previously for any degree or examination at any other university.

I certify that the protocol has been approved in accordance with the Human Research Ethics Committee (Medical) at the university of the Witwatersrand, Johannesburg (clearance certificate (M180628).

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Article:

A COMPARISON OF MALIGNANT HISTOPATHOLOGICAL DIAGNOSES ON UTERINE CURETTINGS AND HYSTERECTOMY SPECIMENS

Journal: South African Journal of Obstetrics and Gynaecology (currently undergoing peer review)

Submitted in submissible form (manuscript reference SAJOG02078)

Authors	Name	Signature	Date
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DEDICATION

I would like to dedicate this to:

My family, for their unwavering support and encouragement.

My close friends and neighbours, for keeping me sane and grounded.

Harold and Sweetpea, for bringing me joy and for keeping me kind.

PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT

This paper was submitted on 01 October 2021 to the South African Journal of Obstetrics and Gynaecology (SAJOG) ; manuscript number SAJOG02078.

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o Human Gene Mapping Workshop (HGMW): genetic notations and symbols
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o OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
o Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counsellors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

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• May include up to 3 illustrations or tables.
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o Objectives: what the study intends to find out
o Methods: must include study design, number of participants, description of the research tools/instruments, any specific analyses that were done on the data.
o Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they

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• When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
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ABSTRACT

Background. Endometrial carcinoma (EC) is a common gynaecological malignancy in postmenopausal females. Diagnosis is made on endometrial biopsy, where histological subtype and tumour grade are used to predict disease progression and to plan surgical management.

Objectives. We aimed to determine the accuracy of preoperative biopsies compared to the final diagnosis on hysterectomy specimens in our department.

Methods. This was a retrospective, cross sectional study in which 126 biopsies and corresponding hysterectomy specimens, over a 3-year period, were reviewed. Patient demographics and histological features were recorded and statistically analysed.

Results. The most prevalent tumours were endometrioid endometrial carcinoma (EEC) (48.5%), serous carcinomas (25.4%) and carcinosarcomas (16.7%). The majority (66.7%) of tumours were high-grade tumours on biopsy and hysterectomy specimens (58.7%). EECs had a poor sensitivity level (65.12%) compared to other subtypes but had a high specificity rate 90%. There was moderate agreement between biopsy and excision specimen diagnoses. High-grade tumours had a high sensitivity (94.29%) level.

Conclusions. Our study showed moderate agreement between histopathological diagnoses on biopsy, and excision specimens. EEC was the most prevalent tumour subtype. There was a high sensitivity (94.29%) level for biopsies of high-grade tumours, concordant with other studies. The sensitivity of low-grade EECs (42-46%) was lower than international studies, likely due to the comparatively low prevalence of EECs in our population. Accurate preoperative tumour subtyping and grading are needed to guide surgical management. It is envisaged that use of a combined histological and molecular tumour classification will better guide patient treatment and allow for reproducible results.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor Dr Reubina Wadee for her patience, encouragement and support through the entire research process. Her presence was invaluable in the completion of this MMed.

I thank our departmental staff, especially Mr. Abel Ndlovu and Ms. Fadila Ebrahim, for help with retrieving my research data and slides and Dr Gill Henry for assistance with statistical analysis.

The biggest thanks goes to my family, for their support and encouragement during this research project.

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NOMENCLATURE

ARID	AT-rich interaction domain
BRCA	Breast Cancer gene
CMJAH.	Charlotte Maxeke Johannesburg Academic Hospital
DD&C	Diagnostic dilatation and curettage
EC	Endometrial carcinoma
EEC	Endometrioid endometrial carcinoma
EIN	Endometrial intraepithelial neoplasia
ER	Oestrogen receptor
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
IHC	Immunohistochemistry
KRAS	Kirsten rat sarcoma viral oncogene homolog
MMMT	Malignant Mixed Müllerian tumours
MMR-d	Mismatch repair deficient
NEC	Neuroendocrine carcinoma
NHLS	National Health Laboratory Services
Pax 8	Paired-homeobox gene 8
PTEN	Phosphatase and tensin homolog,
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3- Kinase Catalytic Subunit Alpha
POLE	Polymerase epsilon
POLEmut	POLE mutant
PR	Progesterone receptor
SNOMED	Systematized Nomenclature of Medicine
TCGA	The Cancer Genome Atlas
WHO	World Health Organisation

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW:

1.1 Introduction:

Endometrial carcinoma is the sixth most common gynaecological malignancy and the fourteenth leading cause of cancer related deaths worldwide.[1] The incidence varies between 1 to 30 per 100 000 women globally. Higher rates have been reported in developed countries, such as the United States of America and Canada, whereas lower rates are reported in Sub-Saharan Africa, the Middle East and central Asia.[2] In South Africa, the number of uterine malignancies diagnosed in 2017 was 1152, corresponding to 3.8% of all carcinomas diagnosed in females that year.[3] In South Africa, an increased prevalence of risk factors associated with increased oestrogen exposure is expected, mainly due to escalating rates of obesity and decreased fertility. This may result in a greater incidence of endometrial carcinoma in the future.[4] Endometrial carcinoma usually presents with post-menopausal bleeding and is diagnosed on endometrial biopsy. The histological grade assigned on biopsy guides surgical intervention required for definitive staging and management.[5] The accuracy of the biopsy is therefore an important determinant for both diagnosis and management.

1.2 Grading and Histological Subtypes

Endometrial carcinomas have traditionally been divided into two types according to their pathogenesis, as initially described by Bokhman.[6]

1.2.1 Type 1/ endometrioid endometrial carcinoma

Type I or endometrioid endometrial carcinoma (EEC) develops due to excess oestrogen stimulation in the background of endometrial hyperplasia. This is the most common histological type, comprising approximately 80% of all endometrial carcinomas. There is evidence to suggest that carcinogenesis is a multistep process that begins with endometrial hyperplasia without atypia, which progresses to atypical hyperplasia, then endometrial intraepithelial neoplasia (EIN) and finally progresses to invasive carcinoma.[7–9] These tumours may be treated with progestins, especially in females who wish to preserve fertility.[7] EEC is graded as per the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) according to the tumour architecture and proportions of solid and glandular areas. Tumours that have <5% solid growth are considered grade 1 tumours; whereas tumours with 6-50% solid growth are grade 2 tumours, and those with >50% solid

growth are grade 3 tumours. Grade 1 and 2 tumours are considered low-grade neoplasms and usually involve less than 50% of the myometrium, have < 10% likelihood of lymph node metastasis and have an average 90% five-year survival rate.[8] The tumour grading system allows for an increase in the grade if significant nuclear atypia is seen in more than 50% of tumour.[10] There are some prognostic differences between grade 1 and 2 EEC, including a higher risk of recurrence and mortality for grade 2 tumours.[11] Both grades 1 and 2 EECs are treated identically in terms of adjuvant chemotherapy and radiation and are therefore, often combined into the category of 'low-grade' tumours.[8]

1.2.2 Type 2/ non-endometrioid endometrial carcinoma

Type II or non-endometrioid endometrial carcinomas encompass the remaining 10–20% of endometrial malignancies. The two major subtypes in this category are serous carcinoma and clear-cell carcinoma. These cancers often progress from an atrophic endometrium to the precursor lesion, endometrial glandular dysplasia, and then into invasive carcinoma. These tumours are considered high-grade neoplasms by definition.[9]

1.2.3 Histological subtypes

The most recent World Health Organisation (WHO) Classification of Tumours of Female Reproductive Organs includes the following histological types based on morphological patterns of growth: endometrioid, serous, clear cell, neuroendocrine, mixed carcinoma, undifferentiated and dedifferentiated carcinomas.[8]

EECs can display a variety of growth patterns, including acinar, papillary, mucinous and solid, all having a common luminal border. These tumours however, lack the nuclear hobnailing seen in serous carcinomas. 'Hobnailing' refers to the appearance of apical tumour nuclei bulging into the luminal spaces of glands.

Mucinous endometrial carcinomas are a subtype of EEC which show mucinous differentiation in more than 50% of the tumour. The architecture is glandular or villous and composed of columnar cells with minimal stratification. The mucin appears as intracytoplasmic basophilic secretory material. There is usually only mild nuclear atypia and low mitotic activity. These tumours are low-grade and have a good prognosis.[8]

Serous carcinomas are prototypical type II tumours that are characterized by a complex papillary architecture with diffuse, marked nuclear pleomorphism. The cells have enlarged

nuclei with scant cytoplasm, imparting a scalloped appearance to the luminal surface. There is usually extensive necrosis and mitotic activity with areas of psammomatous calcification and myometrial invasion. Immunohistochemically, serous carcinomas show diffuse positive staining (in ≥80% of tumour cells) or complete negative nuclear staining with a p53 antibody. In addition, serous carcinomas display block-like p16 expression and there is an absence of hormone receptors, such as oestrogen and progesterone receptors, which can be used to differentiate serous carcinoma from papillary areas of an EEC. Wilms tumour-1 (WT-1) immunohistochemical staining may be used to differentiate endometrial serous carcinoma from an ovarian serous carcinoma, in which it is positive.[7,8]

Clear cell carcinoma is composed of large cells with distinct cellular membranes that have large amounts of glycogen. The tumour displays tubulocystic, papillary or solid architectural patterns. Papillary projections and hobnailing of tumour nuclei are similar to that seen in clear cell ovarian tumours.[8]

Mixed epithelial and mesenchymal tumours include adenosarcomas and carcinosarcomas. Adenosarcomas have a benign or atypical epithelial component and a low grade malignant stromal component. These tumours are papillary to polypoid neoplasms that project into cystically dilated glandular lumina. The stroma is cellular and may show stromal overgrowth. There may be heterologous differentiation, which is defined by areas of tumour that have malignant stromal mesenchymal elements that are not usually present at that site (such as cartilage or skeletal muscle).[7] Carcinosarcomas are biphasic tumours composed of high-grade malignant carcinomatous and stromal elements. Carcinosarcomas may be associated with previous tamoxifen use and pelvic radiation. The two malignant components are usually sharply demarcated. The epithelial component may be an endometrioid or serous carcinoma. The malignant mesenchymal component is usually a high-grade, non-specific sarcoma but may show heterologous elements (including cartilage, adipose tissue, skeletal muscle or bone). Deep myometrial and lymphovascular invasion is common.[8]

1.3 Immunohistochemistry

Immunohistochemical stains can be used for both diagnostic and prognostic purposes in endometrial carcinoma.

Oestrogen receptor (ER) and progesterone receptor (PR) nuclear staining are usually identified in low-grade tumours but are lost in high-grade tumours. Other nonspecific stains that are positive in endometrial carcinomas include cytokeratin, vimentin and Paired-homeobox gene 8 (Pax 8).[7]

P53 immunohistochemistry is a surrogate marker used to predict the *TP53* mutation status of a tumour. 'Wild-type' nuclear staining is seen in EEC while diffuse positive staining (≥80% of tumour cells) or negative staining is seen in serous carcinoma, which implies a 'mutated' *TP53* gene. Cytoplasmic P53 accompanied by variable nuclear staining is associated with a loss of function mutation resulting from mutations that involve the nuclear localization domain of the p53 protein.[12]

Hypermutated endometrial carcinomas are characterized by microsatellite instability due to dysfunction of one or more of the enzymes involved in DNA repair. Surrogate tests for these tumours include immunohistochemical stains: MLH1, PMS2, MSH2 and MSH6. Beyond prognostication, molecular subtyping can be further used to guide treatment and may be of use as precision medicine evolves. This includes lymph node dissection and adjuvant chemotherapy and radiation in patients previously assessed as being low risk with an unfavourable molecular risk assessment. This has shown to improve overall survival and reduce risk of recurrence.[13,14] Of note, 3-4 % of endometrial carcinomas arise in patients with Lynch syndrome which can be screened for using these immunohistochemical (IHC) markers as a surrogate for mismatch repair deficiency. [7,15]

HER2 protein overexpression has been demonstrated in 25-30% of serous carcinomas, which may then be a focus for targeted therapy in the future. However, HER2 testing by IHC is not yet routinely performed due to differences in interpretation and testing algorithms.[16] Amplification of HER2 correlates with a higher histological grade, greater stage of disease and worse overall outcome.[17]

1.4 Epidemiology

1.4.1 Age

Most (80%) women with endometrial carcinoma are postmenopausal at diagnosis.[7] However, endometrial carcinoma may develop in any age group. Tumours that occur in younger, premenopausal women present at an earlier stage and tend to be of a lower histological grade.[18]

1.4.2 Risk factors

Risk factors for type 1 endometrial carcinoma include: obesity, hypertension, diabetes mellitus, ovulatory dysfunction, dysfunctional bleeding, infertility and long-term oestrogen or tamoxifen use; all of which are associated with raised levels of circulating oestrogen. Risk factors for type 2 endometrial carcinoma are not well recognized. These tumours often present in post-menopausal women who are multiparous and are smokers.[7]

1.5 Histopathological diagnosis

The determination of histological subtype and grade in biopsy specimens are important factors in predicting disease progression and outcome. These factors correlate with the depth of myometrial invasion, lymph node involvement, surgical stage, and overall patient survival.[19] Due to the fact that these parameters can only be assessed once the entire tumour has been excised, there is a reliance on the histological grade and/or tumour subtype assigned on the biopsy specimen to guide the extent of the surgical intervention.[20] The relatively small amount of tissue in relation to volume of formalin in biopsy specimens results in better tissue fixation and allows for adequate morphological assessment and immunohistochemical staining, as target antigens are better preserved in contrast to the final hysterectomy specimen which is often less well-fixed.[21]

The initial clinical investigation includes a transvaginal ultrasound followed by an endometrial sample. An ultrasound endometrial thickness of greater than 4mm is clinically concerning for malignancy and requires biopsy in post-menopausal women who are not on Tamoxifen. If an ultrasound is not available, a "blind" sample may be performed without guidance.[22] The histopathological diagnosis is made on a variety of preoperative biopsy methods, including hysteroscopy and biopsy, Pipelle sampling and diagnostic dilatation and curettage (DD&C). In South Africa, the Pipelle sample is most used as it is an easily accessible and economical method. It is performed on an outpatient basis, does not require general anaesthesia and is less invasive than DD&C. It has been demonstrated that the Pipelle has sensitivity levels of between 84.2% to 99% in detecting endometrial pathology.[4,23]

As endometrial carcinoma may form broad based polypoid masses or infiltrate diffusely into the myometrium, the tumour may be missed on undirected biopsies. Hysteroscopy

may be beneficial in such cases to visually appreciate and direct biopsies more accurately.[24]

A meta-analysis by Clark *et al* [25] showed an accuracy of up to 99% in the diagnosis of endometrial carcinoma with the use of the Pipelle. However, accuracy was variable amongst the twelve studies analysed. Benign diseases (including endometrial polyps) were found to be less accurate than malignant diagnoses.[25] Hysteroscopy allows for direct visualization and biopsy which results in greater accuracy than Z-samples, especially of focal lesions.[26] A meta-analysis by van Hanegem *et al*,[27] showed a sensitivity of close to 100% for DD&C and 90% for hysteroscopic guided biopsy. The failure rate of endometrial sampling with the above methods was 11% (mostly due to cervical stenosis) and insufficient samples in 31% of cases. A diagnosis of atypical hyperplasia or carcinoma was found in 7% of these failed or insufficient cases, highlighting the need for repeat biopsies in these patients. A similar study by Moradan *et al* [28] showed a relatively high sensitivity of 83.3% using DD&C for the diagnosis of endometrial pathology with a lower sensitivity rate in the detection of benign lesions such as polyps or hyperplasia (62%). Another study has shown increased sensitivity rates of biopsies that had high grade tumours as compared to low grade tumours (99.2% and 93.8% respectively).[29]

In South Africa, both epidemiological data regarding endometrial carcinoma and data regarding diagnostic accuracy is lacking with only one study to date performed by Mhlongo *et al.*[4] Mhlongo *et al* showed similar sensitivity rates of 93.8% for low grade endometrioid tumours and 99.2% for high grade endometrioid tumours. A lower sensitivity was noted for non-endometrioid subtypes. However, up to 50% of endometrioid tumours were not graded on biopsy.[4] The patients who had unspecified grades of tumour could possibly have been offered further surgical staging by lymph node dissection at the time of hysterectomy if a definitive histological tumour grade was provided. Adjuvant treatment may also have been delayed, and low risk patients may have been overtreated.

A study by Helpman *et al* concluded that preoperative endometrial sampling was only a modest predictor of final surgical pathology findings and may underestimate the risk of disease spread and recurrence.[5] These conflicting findings suggest that more studies should be undertaken to assess the accuracy of endometrial biopsies, especially in the South African setting, which may demonstrate different findings to studies conducted abroad. These may include population specific differences in tumour genetics and

prevalence. In addition, suboptimal resource allocation has effects on surgery and diagnostic equipment and a lack of ancillary tests available to pathologists may also affect the diagnostic process.

1.6 Staging and Treatment

Staging by the FIGO system requires dissection of para-aortic and pelvic lymph nodes for high-grade tumours.[10] Unnecessary surgery by lymph node dissection may cause significant morbidity, including intraoperative and postoperative complications such as lymphoedema, loss of fertility and endogenous hormone production by the ovaries, as well as extended surgical time and associated costs.[21]

Pathological tumour stage is generally only rendered after hysterectomy as biopsies do not allow for assessment of depth of myometrial invasion. The pathological stage determines a patient's need for adjunctive therapy. For staging purposes, the depth of invasion into the myometrium is divided into more than, or less than 50%. True myometrial extension should be differentiated from expansion of the endometrial-myometrial junction and from atypical or malignant changes involving pre-existing foci of adenomyosis.[30]

Extension of tumour cells into the cervix occurs in approximately 10% of cases.[7] Lymphovascular invasion is the most important route of spread. With EECs**,** the main route of spread is via the pelvic and para-aortic lymph nodes and the ovaries. Nodal metastases are more common in high-grade tumours, tumours that are large in size, deeply invasive or involve the cervix.[31] Serous carcinoma, however, usually spreads via lymphatics. Peritoneal spread tends to occur early in disease and hence the tumour has a more aggressive behaviour.[8]

Indications for lymph node dissection include: >50% myometrial invasion, grade 3 tumour, cervical stromal involvement, extrauterine spread, unfavourable histological components (serous, clear cell or undifferentiated carcinoma) and palpably enlarged nodes.[7] Recent recommendations include radiation therapy in addition to chemotherapy for high-risk serous carcinoma or advanced stage disease.[13]

The treatment of EEC includes progestin therapy or if indicated, a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The treatment of serous carcinoma includes a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy,

peritoneal cytology and biopsy of pelvic and para-aortic lymph nodes. This is followed by adjuvant chemotherapy and/or radiation therapy.[7]

1.7 Molecular alterations

The major genetic mutations that occur in endometrioid endometrial carcinomas include: microsatellite instability (MSI) (28%), mutations in Phosphatase and tensin homolog *(PTEN),* Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha *(PIK3CA)* gene, Kirsten rat sarcoma viral oncogene homolog *(KRAS)* gene and the Beta catenin gene. The genetic mutations that characterize serous endometrial carcinomas are TP53 and heterozygosity loss. Many of these genes function as tumour suppressor genes and therefore loss of function mutations contributes to genomic instability. Other affected pathways (including the AT-rich interaction domain (*ARID*) mutations and the *PTEN* pathway), have also been recently described due to upstream or downstream effects on the major mutation mechanisms. These genetic mutations may help in the diagnosis, classification and targeted therapy of endometrial carcinomas in the future.[17,32]

There has been an increased understanding of the molecular basis of endometrial carcinoma as a result of The Cancer Genome Atlas (TCGA) assessment of endometrial carcinomas. [7] Subsequently, a molecular classification has been shown to be significantly prognostically more reproducible than conventional subtyping by morphological assessment alone. Histological subtyping shows significant interobserver variability and does not always correlate with survival rates.[12] TCGA classification divides tumours into the following subgroups: 1) polymerase epsilon (POLE) ultramutated 2) hypermutated microsatellite instability 3) copy number low and 4) copy number high ("serous-like"). [33,34] The classification confirmed that low copy number and POLE mutations have a favourable outcome and correspond to "type 1" endometrial carcinomas. High copy number and *TP53* mutations are highly aggressive and are comparable to "type 2" tumours. MSI unstable and copy number low tumours have an intermediate prognosis.[35] This molecular method of classification is costly, especially in resource limited settings such as South Africa. Therefore, its widespread use has not yet been adopted in developing countries.

1.8 Prognosis

Most (80%) endometrial carcinomas are diagnosed early and have a 5-year survival rate of greater than 95%. This decreases to 68% for cases in which there is regional spread and 17% for cases with distant metastatic disease.[4]

Favourable prognostic factors include: Tumours with FIGO stage I or II diseases, <50% myometrial invasion, low histological grade, no lymphovascular invasion and ultramutated molecular subtypes. Prognostic factors considered to be unfavourable include: tumours with FIGO stage III or IV disease, >50% myometrial invasion, high histological grade, older age, lymphovascular space invasion and copy number high molecular subtypes.[7]

1.9 Conclusion:

With the socioeconomic transition that is occurring in many developing countries, including South Africa, it is expected that the prevalence of risk factors and hence the prevalence of endometrial carcinoma will increase. There will therefore be a greater need for cost effective and accurate diagnostic procedures that can be used in resource limited settings. Wherever possible, it is important to accurately grade the preoperative biopsy to decrease the unnecessary complications of radical surgery. Histological findings, including the grade and staging of endometrial carcinomas are essential predictors of disease outcome and lymph node involvement. Many gynaecological surgeons rely on the preoperative biopsy in determining management of patients with malignant disease. While there is an intensification in interest of the molecular classification of endometrial tumours, ultimately a combined histological and molecular approach is likely to be used in the South African setting. In African countries, including South Africa, there is still a heavy reliance on morphological diagnosis at biopsy, with current data regarding the accuracy of these biopsies being limited. As such, this study aimed to determine the accuracy of preoperative biopsies compared to the final diagnosis on hysterectomy specimens in our department, which may show different findings to the current literature which is sparse in the South African and African context.

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CHAPTER 2: SUBMISSABLE ARTICLE

A COMPARISON OF MALIGNANT HISTOPATHOLOGICAL DIAGNOSES ON UTERINE CURETTINGS AND HYSTERECTOMY SPECIMENS

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2.1 Abstract

Background: Endometrial carcinoma (EC) is a common gynaecological malignancy in postmenopausal females. Diagnosis is made on endometrial biopsy, where histological subtype and tumour grade are used to predict disease progression and to plan surgical management.

Objectives: We aimed to determine the accuracy of preoperative biopsies compared to the final diagnosis on hysterectomy specimens in our department.

Methods:

This was a retrospective, cross sectional study in which 126 biopsies and corresponding hysterectomy specimens, over a 3-year period, were reviewed. Patient demographics and histological features were recorded and statistically analysed.

Results:

The most prevalent tumours were endometrioid endometrial carcinoma (EEC) (48.5%), serous carcinomas (25.4%) and carcinosarcomas (16.7%). The majority (66.7%) of tumours were high-grade tumours on biopsy and hysterectomy specimens (58.7%). EECs had a poor sensitivity level (65.12%) compared to other subtypes but had a high specificity rate 90%. There was moderate agreement between biopsy and excision specimen diagnoses. High-grade tumours had a high sensitivity (94.29%) level.

Conclusions:

Our study showed moderate agreement between histopathological diagnoses on biopsy, and excision specimens. EEC was the most prevalent tumour subtype. There was a high sensitivity (94.29%) level for biopsies of high-grade tumours, concordant with other studies. The sensitivity of low-grade EECs (42-46%) was lower than international studies, likely due to the comparatively low prevalence of EECs in our population. Accurate preoperative tumour subtyping and grading are needed to guide surgical management. It is envisaged that use of a combined histological and molecular tumour classification will better guide patient treatment and allow for reproducible results.

2.2 Introduction and Background

Endometrial carcinoma (EC) is the sixth most common gynaecological malignancy and the fourteenth leading cause of cancer related deaths worldwide.[1] Uterine malignancies accounted for 3.8% of all malignancies in South African females in 2017.[2]

EC usually presents with post-menopausal bleeding. Initial investigation includes a uterine ultrasound evaluation, with an endometrial thickness >4mm considered to be concerning for malignancy.[3] In South Africa, the Pipelle/"Z-Sample" is a cost effective method that is performed on an outpatient basis and has a sensitivity of 84.2% to 99%.[4–6]

Endometrial carcinomas have previously been grouped into Type I and Type II tumours. Endometrioid endometrial carcinoma (EEC) is the typical Type I tumour which arises in the background of endometrial hyperplasia. Risk factors for EEC are obesity, Tamoxifen usage, hormone replacement therapy and decreased fertility; all of which are associated with increased circulating oestrogen.[7,8] These tumours develop from endometrial hyperplasia without atypia, progress to atypical hyperplasia, followed by endometrial intraepithelial neoplasia (EIN) and finally to invasive carcinoma. Type II or non-endometrioid endometrial carcinoma, is by definition high-grade and is the umbrella category for serous and clear cell carcinomas. These occur in multiparous, post-menopausal women, often in the background of an atrophic endometrium. Type II tumours develop in a background of endometrial glandular dysplasia, progress to serous intraepithelial carcinoma and then become invasive serous carcinomas.[8,9] Other histopathological subtypes of endometrial carcinoma include carcinosarcoma,

neuroendocrine carcinoma (NEC), undifferentiated and dedifferentiated carcinomas, all of which are high grade by definition.[10]

ECs are histologically graded, which aids in prognostication and guides the extent of surgical intervention.[11] Low-grade tumours are treated fairly conservatively whereas high-grade tumours require more aggressive forms of treatment including radical lymph node dissection, chemotherapy, radiation therapy and omental biopsy.[8] FIGO staging also requires assessment of para-aortic and/or pelvic lymph nodes for high-grade or locally advanced tumours.[12] Lymph node dissection may cause significant morbidity, including intraoperative complications, postoperative lymphoedema and deep vein thrombosis.[13] Apart from grade and histological subtype which may be assigned on biopsy, most prognostic factors of EC can only be assigned following examination of the hysterectomy specimen. As such, there is a reliance on accurate grading and subtyping of endometrial biopsies to facilitate adequate planning of surgical intervention and chemoradiation.

Our study aimed to determine the accuracy of histopathological findings of preoperative endometrial biopsy specimens compared to pathology results of the final hysterectomy specimens. In addition, we aimed to expand on the limited South African data available regarding the prevalence of histological subtypes, grade and demographics in patients diagnosed with EC.

2.3 Methods

The was a retrospective, cross-sectional study. Ethical clearance was granted by the Human Research Ethics Committee (Medical), University of the Witwatersrand, (certificate number M180628). One hundred and twenty-six (126) biopsies with corresponding hysterectomies diagnosed between 1 January 2015 to 31 December 2017, at the Department of Anatomical Pathology, University of the Witwatersrand/ National Health Laboratory Services (NHLS) Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) were reviewed. The NHLS database was searched using the Systematized Nomenclature of Medicine (SNOMED) codes for appropriate terms.

Exclusion criteria encompassed the following: cases where archived slides could not be found, incomplete or partially completed reports, and hysterectomy specimens in which the entire tumour was entirely autolyzed.

The glass slides were reviewed independently by both authors; reviewer 1(R1) and reviewer (R2); in the absence of pathology reports. The authors then compared their own results and compared their findings against those of the final pathology reports. Relevant, anonymised data were collected from each case.

IBM SPPS version 23 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Categorical data were recorded as graphs, tables, frequencies, and percentages and means where appropriate. In the assessment of biopsy performance statistics, all cases of atypical cells, 'not applicable' and in-situ malignancies were excluded. Biopsy sensitivity and kappa coefficient scores were used to assess agreement of grading and histological subtype between preoperative and final pathology, with 95% confidence intervals. Conventional methods of interpreting kappa (K) values were used with level of agreement categories of "poor/slight" (K 0.0–0.20), "fair" (K 0.21–0.40), "moderate" (K 0.41–0.60), "strong/substantial"(K 0.61–0.80), "almost perfect"(K 0.81–1.00).[14]

2.4 Results

Table 1 shows that most cases (96.8%) in our cohort were from post-menopausal, multiparous females between 60-79 years of age, and diagnosed as 'malignant' on both biopsy (86.5%) and hysterectomy (97.6%), ($p<0.001$). Most patients (79.4%) had a total abdominal hysterectomy, with a significant number (18.3%) having undergone radical hysterectomies; which included lymph node dissections ($p<0.001$). The mean number of days between biopsy and hysterectomy was 86 days (range:13-281). The majority of patients (87.3%) only required one biopsy, whereas 16 patients (11.9%) required two biopsies and only one patient (0.8%) required three biopsies due to previous biopsies being inadequate for a diagnosis. A mean of 2.6 immunohistochemical stains were used per biopsy (range:0-12) and 1.54 per hysterectomy (range:0-10).

No statistically significant differences were noted in the proportions of myometrial depth of invasion ($p=0.0652$). However, a statistically significant proportion of cases showed no cervical stromal involvement and no lymphovascular invasion ($p<0.001$).

Table 1: Patient demographics and histopathological findings

	n (%)	p-value		n (%)	p-value
Age (years)			**Hysterectomy Type**		
<50	3 (2.4)	<0.001	Radical	23 (18.3)	<0.001
50-59	22 (17.5)		Total	100 (79.4)	
60-69	49 (38.9)		Subtotal	3(2.4)	
70-79	44 (34.9)		**Lymphovascular Invasion**		
>79	8 (6.3)		Present	25 (19.8)	<0.001
Parity			Absent	98 (77.8)	
0	4 (3.2)	<0.001	N/A	3 (2.4)	
1-3	40 (31.7)		**Myometrial Depth of Invasion (%)**		
4-6	19 (15.1)		<50	59 (46.8)	0.652
>6	10 (7.9)		>50	64 (50.8)	
Not specified	53 (42.1)		N/A	3 (2.4)	
Menopausal status			**Cervical Stromal Involvement**		
Pre-menopausal	3 (2.4)	<0.001	Present	37 (29.4)	<0.001
Post-menopausal	122 (96.8)		Absent	82 (65.1)	
Peri-menopausal	1 (0.8)		N/A	7 (5.6)	
Biopsy: IHC used			**Hysterectomy IHC used**		
Yes	72 (57.1)	0.109	Yes	47 (37.3)	0.009
No	54 (42.9)		No	79 (62.7)	
Biopsy: Final Diagnosis			**Hysterectomy: Final Diagnosis**		
Inadequate	3 (2.4)	<0.001	Malignant	123 (97.6)	<0.001
Malignant	109 (86.5)		Atypical	2 (1.6)	
Atypical hyperplasia	7 (5.6)		No tumour	1 (0.8)	
Atypical cells only	7 (5.6)		**Hysterectomy Histological Subtype**		
Biopsy Histological Subtype			Endometrioi	61 (48.4)	<0.001
Endometrioid	34 (27.0)	<0.001	Serous	32 (25.4)	
Serous	41 (32.5)		Clear cell	5 (4.0)	
Clear cell	3 (2.4)		Neuroendoc	1 (0.8)	
Neuroendocrine	1 (0.8)		Carcinosarc	21 (16.7)	
Carcinosarcoma	12 (9.5)		Dedifferenti	3 (2.4)	
Dedifferentiated	2 (1.6)		No tumour	1 (0.8)	
Adenosquamous	1 (0.8)		EIN	2 (1.6)	
Endocervical	1 (0.8)		**Hysterectomy Grade**		
EIN	7 (5.6)		Grade 1	20 (15.9)	<0.001
Not specified	13 (10.3)		Grade 2	19 (15.1)	
N/A	11 (8.7)		High Grade	84 (66.7)	
Biopsy Grade			N/A	3 (2.4)	
Grade 1	12 (9.5)		**Hysterectomy: TNM Stage**		

Grade 2	11 (8.7)	<0.001	**Tumour (T)**		
High Grade	74 (58.7)		1	65(51.6)	<0.001
Not specified	10 (7.9)		2	25(19.8)	
N/A	19 (15.1)		3	33(26.2)	
Hysterectomy: FIGO stage			In Situ (IS)	2(1.6)	
I	64 (50.8)	<0.001	N/A	1 (0.8)	
II	24 (19.0)		**Lymph Nodes (N)**		
III	33 (26.2)		0	16 (12.7)	0.102
IV	1 (0.8)		1	8 (6.3)	
In Situ (IS)	2 (1.6)		N/A	102 (81.0)	
No Tumour	1 (0.8)		**Metastasis**		
			1	2 (1.6)	<0.001
			X	124 (98.4)	

N/A= not applicable in the case of inadequate biopsy, atypical hyperplasia, or atypical cells only; EIN=Endometrial Intraepithelial Neoplasia. IHC = Immunohistochemistry. The chi-square goodness-of-fit test was used in the assessment of significance.

2.4.1 Histological Subtype

Table I shows that the most prevalent histological subtypes on biopsy specimens were serous carcinoma (32.5%), EEC (27%), and carcinosarcoma (9.5%). In a significant number of biopsies, no histopathological tumour subtype was specified (10.3%), ($p<0.001$). On the excision specimens however, most (48.5%) tumours were EEC, 25.4% were serous carcinomas and 16.7% were carcinosarcomas, ($p<0.001$) (Table 1, Figure 1). Of the 7 tumours diagnosed as atypical hyperplasia on biopsy, 6 were upgraded to a grade 1 or 2 invasive endometrioid carcinoma on the excision specimens, while one case was interpreted as atypical hyperplasia within a polyp, on the hysterectomy specimen.

2.4.2 Histological Grade

Table 1 shows that the majority (66.7%) of tumours were high-grade tumours on both biopsy and hysterectomy specimens (58.7%); ($p<0.001$), while 7.9% of biopsies did not have a FIGO grade assigned.

2.4.3 Agreement

There was a kappa value of 0.529 when the biopsy histology subtype was compared to the final histology subtype and a value of 0.530 (moderate agreement) was obtained for comparison of FIGO grade between the biopsy and excision specimens. High-grade

tumours had a higher sensitivity (94.29%) and were more common than low-grade tumours. Table 2 shows the performance statistics of biopsy accuracy. An almost perfect level of agreement was found between: R1's assessment of tumour subtype on biopsy and the hysterectomy specimen (k=0.95), whereas R2 had kappa scores of (k=0.94) and (k=0.89) for assessment of grade on hysterectomy specimens and on biopsies respectively(k=0.89). Both R1 and R2 had substantial agreement with biopsy histological subtype (k=0.73 and 0.69).

Table 2: Summary of biopsy performance statistics

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)	Accuracy
Grade						
Grade 1	41.67	92.77	45.45	91.67	12.63	86.32
Grade 2	46.15	93.90	54.55	91.67	13.68	87.37
Grade 3	94.29	72.00	90.41	81.82	73.68	88.42
Histological Subtype						
Endometroid	65.12	90.00	84.85	75.00	46.24	78.49
Serous	77.78	71.21	52.50	88.68	29.03	73.12
Clear cell	66.67	98.89	66.67	98.89	3.23	97.85
Neuroendocrine	100.00	100.00	100.00	100.00	1.08	100.00
Carcinosarcoma	55.56	97.33	83.33	90.12	19.35	89.25
Dedifferentiated	100.00	98.91	50.00	100.00	1.08	98.92

2.5 Discussion

Our study showed moderate overall agreement between diagnosis on endometrial curettings and the final excision specimen with regards to biopsy grade and histological subtype respectively, which is concordant with or better than other studies. [6,13,15] We showed a high level of sensitivity when comparing biopsies that had high-grade tumours (94.29%), which is also concordant with other studies. However, the sensitivity of grade 1 and 2 EEC (42-46%) is lower than reported in these international studies, likely due to the comparatively low prevalence of low-grade tumours in our population. [6,13,15] Helpman et

al.[11] showed similar levels of agreement to our study and concluded that preoperative endometrial sampling was a modest predictor of final surgical pathology findings.

Visser et al.[15] however, showed a higher degree of overall agreement with the lowest agreement rate for EEC, similar to our findings. This study showed that 25% of tumours were histologically downgraded to grade 1 or 2 tumours and 21% were upgraded to high-grade tumours. In our study, of the six tumours that were histologically upgraded, three were upgraded from EEC grade 1 to EEC grade 3. Four tumours were downgraded significantly, with three of these having been downgraded from high-grade serous carcinoma to EEC grade 1. One tumour was downgraded from EEC grade 3 to EEC grade 1. For both histological upgrades and downgrades, this was due to better tissue preservation and visual representation of the tumour on the hysterectomy specimens. In addition, the larger tumour volume on the excision specimens allowed for improved assessment of cytomorphological features and solid or papillary growth patterns, which are integral to assigning a tumour FIGO grade.

Despite EEC having had a relatively poor sensitivity (65.12%) compared to other subtypes, EEC had a high specificity rate (90%) and was the most prevalent tumour subtype; whereas NEC and dedifferentiated carcinoma had sensitivity and specificity levels of 100% but were the most uncommon malignancies. Of the most prevalent subtypes, serous carcinoma had the highest sensitivity of 77.68% compared to EEC and carcinosarcoma. EEC had a comparatively poor biopsy sensitivity, but had a high specificity compared to serous carcinoma. This shows that interpretation of the level of agreement is most meaningful for high-grade tumours and highly prevalent tumour subtypes.

Although EEC was the most common subtype on excision specimens, serous carcinoma was the most commonly diagnosed subtype on biopsy (32.5%). Thus, EECs and carcinosarcomas are under-diagnosed while serous carcinomas are over-diagnosed on biopsy specimens at our institution. The most likely reason for this is that solid areas seen in EEC are better assessed on hysterectomy specimens and may not be adequately sampled and represented on biopsy specimens. High grade EEC may also show papillary-like growth patterns and nuclear ‘hobnailing’, which may account for the tumour being diagnosed as a serous carcinoma on biopsy, despite the final diagnosis being that of high-grade EEC. In the case of carcinosarcoma, sarcomatous areas and heterologous elements are more likely to be sampled and better represented on the excision specimen. In addition,

there may be a difference in diagnostic thresholds for patterns of growth, nuclear grade or immunohistochemical staining between pathologists. Gilks et al. showed a considerable level of disagreement (up to 35.8%) when comparing histological diagnoses by various pathologists. The most common disagreements were between serous and high-grade EEC.[16]

Only one other South African study to date, by Mhlongo et al, has assessed concordance rates between endometrial biopsies and excision specimens.[4] Mhlongo et al. showed high sensitivities (93.8%) for low-grade endometrioid tumours and 99.2% for high-grade endometrioid tumours. Our study however, showed higher sensitivities (65.65%) for serous carcinoma compared to Mhlongo et al (42.9%). This may be due to the larger sample size in our study. Our cohort showed that EECs form a significantly lower proportion (48%) of total cases, with an increased prevalence of serous carcinoma in our population, consistent with findings by Mhlongo *et al*. This contrasts to international studies (in which EEC accounts for 80-90% of cases), but is consistent with the fact that serous carcinomas are more common in multiparous females and in African populations.[4,8] While risk factors for the development of serous carcinoma are not well established, *TP53* mutations are the underlying molecular abnormality. Risk factors such as previous pelvic radiation and germline mutations, for example mutations in the Breast Cancer gene (*BRCA*), warrant further investigation in our population.[10]

The Cancer Genome Atlas (TCGA) have now classified ECs into four groups according to their molecular make-up, which has been prognostically reproducible and allows for better prediction of patient outcomes than the traditional dualistic classification.[17] The TCGA groups include: *POLE* mutant (POLEmut), (associated with a good prognosis); mismatch repair deficient (MMR-d); low-copy-number alterations, (both of which are associated with an intermediate prognosis) and high-copy number variant and *p53* mutant (p53mut); which are associated with a poor prognosis.[18] Unfortunately, a full molecular work-up and classification in a resource constrained setting such as in state hospitals of South Africa, is not always feasible. However, partial classification is possible with the use of immunohistochemical (IHC) stains such as p53 and MMR proteins, which are available in some South African anatomical pathology laboratories. These may be used to classify ECs as serous carcinomas or MMR deficient carcinomas and thus aid in prognostication. More immunohistochemical stains were used for biopsies compared to hysterectomy specimens in our study, as these stains are required for initial diagnosis and are usually not needed if

the findings on hysterectomy are morphologically consistent with those of the biopsy. In our cohort, of the seven cases that had significant changes in tumour grades, only one case had p53 and MMR immunohistochemistry. Studies have shown IHC use to significantly improve agreement between biopsy and hysterectomy.[18] P53 is an immunohistochemical stain which serves as a surrogate marker for underlying *TP53* mutation and is currently the most frequently used stain to identify *TP53* mutant neoplasms such as serous carcinomas. However, *Polymerase E* assessment is not performed in most state hospitals. As stated previously, PolE ECs have the best prognosis, whilst p53 mutant ECs fare the worst, whereas MMRd and copy-number low tumours have an intermediate prognosis.[12,19] Using p53 and MMRd IHC stains routinely may help improve the accuracy of diagnosis, especially in the case of EECs. An integrated clinical, morphological and molecular classification, where available, may identify previously uncategorized high-risk patients who require individualized treatment such as fertility-sparing surgery and an integrated risk stratification that guides use of brachytherapy, external beam radiation and chemotherapy for high-risk tumours.[20]

Our study showed that 73.7% of tumours were high-grade ECs on biopsy but only 19% of patients underwent radical surgical intervention. The low rate of radical surgery for high-grade tumours in our study suggests that the American Joint Committee on Cancer and the International Union for Cancer Control update the tumour-node-metastasis (TNM) Classification of Malignant Tumours and FIGO stage may not be an accurate reflection of the actual tumour stage in our population as the lymph nodes had not been surgically excised and were therefore not microscopically examined. Although our study was performed at a quaternary hospital complex, our department provides a pathology service to many hospitals and clinics in the southern Gauteng region and not all such health care facilities have gynaecological oncology services or personnel with experience to perform radical surgeries, which may account for the low number of lymph node dissections in patients with high-grade ECs. Other factors which may explain the low number of radical surgeries include the age of patients, as elderly patients with comorbidities may not tolerate the risk of radical surgery. These are all factors that may be discussed at multidisciplinary team meetings to establish the most beneficial, definitive management plans for patients.

Our study serves as a form of quality assurance as it highlights delays in surgery, suboptimal biopsies and unspecified grades (7.9%). It underscores the need for ancillary tests such as IHC to ensure more accurate, reproducible results, especially if grade or

subtype are different on hysterectomy specimens. Only 16% of cases required more than one biopsy before a diagnosis was made, with only 1 patient needing three biopsies, inferring that a diagnosis should be assigned by at least two biopsy specimens. The mean period between biopsy and hysterectomy was of almost three months' duration - 86 days (13-281). Delays in turnaround time of reports, the need for repeat biopsies and lack of surgical resources may have contributed to the relatively lengthy interval of biopsy to surgery. These are factors which may increase patient morbidity and mortality. Other causes of delayed turnaround time include, trainee/registrar training factors (due to the necessity of teaching by pathologists and co-existing responsibilities of registrars), tissue processing factors (including delays in IHC stains) and incomplete clinical information supplied.[21] These may be addressed by improved sampling methods and training to attain adequate biopsies and better communication between pathologists and gynaecologists by raising issues of concern at multidisciplinary team meetings. Complete clinical details and contact numbers should be filled out on the patient requisition forms that accompany tissue specimens and a request to process biopsy specimens as urgent specimens, as opposed to routine cases may also improve workflow and result in faster laboratory processing and reporting.

2.6 Conclusion

Our study showed moderate agreement between histopathological findings on biopsy, (including subtype and grade) and the final hysterectomy specimen results. Gynaecological surgeons rely on the *preoperative biopsy* findings for patient management and thus are dependent on accurate tumour subtyping and grading. It is envisaged that a combined histological and molecular tumour classification should be used, which may better guide overall patient management by producing more accurate and reproducible findings.

2.7 Study limitations, strengths and recommendations

Our study was conducted at a quaternary academic institution within the public sector and as such, may not be extrapolated to the entire South African population as data from the private sector was not included. Study limitations include the fact that clinical information was sourced only from that documented on the histopathology report, which is a reflection of the details provide by the requesting clinician. As such, the type of biopsy equipment used, the type of surgical procedure or other clinical details and patient risk factors were often not routinely included. The retrospective nature of the study could also be viewed as

a limitation as this missing information could have been collected if the study was prospective. Our study assessed agreement of overall tumour grade, and not only grades assigned for EEC as other studies have done. This study contributes to the current sparse data from the African continent and ours is the largest cohort to date, which has compared biopsy and hysterectomy specimen findings. While advances are made in the molecular classification of tumours, the agreement of biopsy with hysterectomy findings will continue to be important in resource limited settings.

2.8 Declaration

This study was conducted in partial fulfilment of Dr. Ismail's requirements of an MMed (Anatomical Pathology) degree.

2.9 Acknowledgements

Dr Gill Hendry is thanked for her assistance with the statistical analysis. Ms. Fadila Ebrahim and Mr. Abel Ndlovu are thanked for their assistance in retrieval of slides for review.

2.10 Author contributions

AI performed the data collection, analysis and wrote the manuscript. AI and RW reviewed slides. RW conceived the study, assisted with the write-up, and critically assessed the manuscript.

2. 11 Funding

None.

2.12 Conflicts of interest

None.

2.13 References - Article

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CHAPTER 3: APPENDICES

3.1 Figure 1: Histological subtypes of endometrial carcinoma

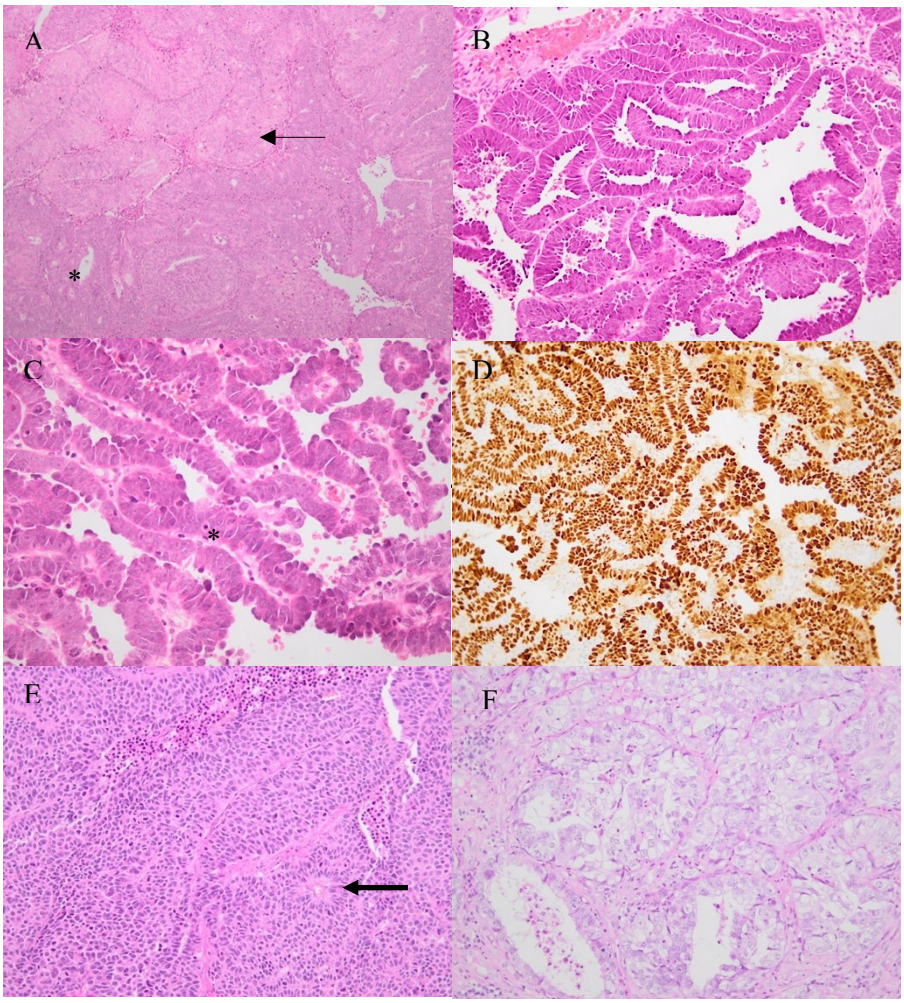

Figure 1: Histological subtypes of endometrial carcinoma:

A. Endometrioid adenocarcinoma: Back-to-back glandular arrangements with solid areas (arrow). Haematoxylin and Eosin (H&E) 100x original magnification.

B. Serous adenocarcinoma: Papillary architecture with markedly atypical cells. H&E 200x original magnification.

C. Serous adenocarcinoma: Papillary cores (*) are lined by cells that show marked nuclear pleomorphism and hobnailing (arrow). H&E 400x original magnification.

D. P53 immunohistochemical stain: Diffuse nuclear staining highlights a mutated TP53 gene, common in serous carcinoma and high-grade EEC. 200x original magnification.

E. Neuroendocrine carcinoma: Nests of tumour cells with rosette formation (arrow) surrounded by delicate blood vessels. H&E 200x original magnification.

F. Clear cell carcinoma: Solid nests of polygonal cells with clear to eosinophilic cytoplasm. H&E400x original magnification.

3.2 TABLES

3.2.1 Table 1: Patient demographics and histopathological findings

	n (%)	p-value		n (%)	p-value
Age (years)			**Hysterectomy Type**		
<50	3 (2.4)	<0.001	Radical	23 (18.3)	<0.001
50-59	22 (17.5)		Total	100 (79.4)	
60-69	49 (38.9)		Subtotal	3(2.4)	
70-79	44 (34.9)		**Lymphovascular Invasion**		
>79	8 (6.3)		Present	25 (19.8)	<0.001
Parity			Absent	98 (77.8)	
0	4 (3.2)	<0.001	N/A	3 (2.4)	
1-3	40 (31.7)		**Myometrial Depth of Invasion (%)**		
4-6	19 (15.1)		<50	59 (46.8)	0.652
>6	10 (7.9)		>50	64 (50.8)	
Not specified	53 (42.1)		N/A	3 (2.4)	
Menopausal status			**Cervical Stromal Involvement**		
Pre-menopausal	3 (2.4)	<0.001	Present	37 (29.4)	<0.001
Post-menopausal	122 (96.8)		Absent	82 (65.1)	
Peri-menopausal	1 (0.8)		N/A	7 (5.6)	
Biopsy: IHC used			**Hysterectomy IHC used**		
Yes	72 (57.1)	0.109	Yes	47 (37.3)	0.009
No	54 (42.9)		No	79 (62.7)	
Biopsy: Final Diagnosis			**Hysterectomy: Final Diagnosis**		
Inadequate	3 (2.4)	<0.001	Malignant	123 (97.6)	<0.001
Malignant	109 (86.5)		Atypical	2 (1.6)	
Atypical hyperplasia	7 (5.6)		No tumour	1 (0.8)	
Atypical cells only	7 (5.6)		**Hysterectomy Histological Subtype**		
Biopsy Histological Subtype			Endometrioid	61 (48.4)	<0.001
Endometrioid	34 (27.0)	<0.001	Serous	32 (25.4)	
Serous	41 (32.5)		Clear cell	5 (4.0)	
Clear cell	3 (2.4)		Neuroendocrine	1 (0.8)	
Neuroendocrine	1 (0.8)		Carcinosarcoma	21 (16.7)	
Carcinosarcoma	12 (9.5)		Dedifferentiated	3 (2.4)	
Dedifferentiated	2 (1.6)		No tumour	1 (0.8)	
Adenosquamous	1 (0.8)		EIN	2 (1.6)	
Endocervical	1 (0.8)		**Hysterectomy Grade**		
EIN	7 (5.6)		Grade 1	20 (15.9)	<0.001
Not specified	13 (10.3)		Grade 2	19 (15.1)	
N/A	11 (8.7)		High Grade	84 (66.7)	
Biopsy Grade			N/A	3 (2.4)	

Grade 1	12 (9.5)	<0.001	**Hysterectomy: TNM Stage**		
Grade 2	11 (8.7)		**Tumour (T)**		
High Grade	74 (58.7)		1	65(51.6)	<0.001
Not specified	10 (7.9)		2	25(19.8)	
N/A	19 (15.1)		3	33(26.2)	
Hysterectomy: FIGO stage			In Situ (IS)	2(1.6)	
I	64 (50.8)	<0.001	N/A	1 (0.8)	
II	24 (19.0)		**Lymph Nodes (N)**		
III	33 (26.2)		0	16 (12.7)	0.102
IV	1 (0.8)		1	8 (6.3)	
In Situ (IS)	2 (1.6)		N/A	102 (81.0)	
No Tumour	1 (0.8)		**Metastasis**		
			1	2 (1.6)	<0.001
			X	124 (98.4)	

N/A= not applicable in the case of inadequate biopsy, atypical hyperplasia, or atypical cells only; EIN=Endometrial Intraepithelial Neoplasia. IHC = Immunohistochemistry. The chi-square goodness-of-fit test was used in the assessment of significance.

3.2.2 Table 2: Summary of biopsy performance statistics

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)	Accuracy
Grade						
Grade 1	41.67	92.77	45.45	91.67	12.63	86.32
Grade 2	46.15	93.90	54.55	91.67	13.68	87.37
Grade 3	94.29	72.00	90.41	81.82	73.68	88.42
Histological Subtype						
Endometroid	65.12	90.00	84.85	75.00	46.24	78.49
Serous	77.78	71.21	52.50	88.68	29.03	73.12
Clear cell	66.67	98.89	66.67	98.89	3.23	97.85
Neuroendocrine	100.00	100.00	100.00	100.00	1.08	100.00
Carcinosarcoma	55.56	97.33	83.33	90.12	19.35	89.25
Dedifferentiated	100.00	98.91	50.00	100.00	1.08	98.92

3.3. RESEARCH PROTOCOL:

A COMPARISON OF MALIGNANT HISTOPATHOLOGICAL DIAGNOSES ON UTERINE CURETTINGS AND HYSTERECTOMY SPECIMENS

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1. INTRODUCTION AND BACKGROUND:

Endometrial carcinoma is the sixth most common gynaecological malignancy and the fourteenth leading cause of cancer related deaths worldwide (1) . The incidence varies from between 1 and 30 per 100 000 women globally. Higher rates have been reported in developed countries, such as the United States of America and Canada, whereas lower rates are reported in Sub-Saharan Africa, the Middle East and central Asia.(2) In South Africa, the number of uterine malignancies diagnosed in 2013 was 1152, corresponding to 3.15% of all carcinomas diagnosed that year (3).

Endometrial carcinomas can be divided into two types secondary to two distinct methods of pathogenesis as described initially by Bokhman(4). Type I or 'endometrioid' carcinoma is due to excess oestrogen stimulation in the background of endometrial hyperplasia. This is the most common type, comprising approximately 80% of endometrial carcinomas. There is evidence to suggest that carcinogenesis is a multistep process that begins with endometrial hyperplasia without atypia, which progresses to atypical hyperplasia and then develops into the precursor lesion, endometrial intraepithelial neoplasia (EIN) (5). Unopposed oestrogen stimulation, especially in postmenopausal women, is a major risk factor in this subtype. Risk factors that cause this unopposed oestrogen stimulation include nulliparity, late menopause, early menarche and obesity (6).

Type II or non-endometrioid endometrial carcinomas include the remaining 10–20% of endometrial malignancies. The two major subtypes are serous carcinoma and clear-cell carcinoma. Both cancers appear to progress from an atrophic endometrium to the precursor lesion, endometrial glandular dysplasia. These tumours are considered high grade by definition (5).

The World Health Organisation (WHO) Classification of Tumours of Female Reproductive Organs (7) classifies endometrial carcinomas under the following types: endometrioid, mucinous, serous, clear cell, neuroendocrine, mixed carcinoma, undifferentiated and dedifferentiated carcinomas.

Endometrioid carcinomas can display a variety of growth patterns, including acinar, papillary and solid types, however, these tumours lack the nuclear features of serous carcinoma. They are primarily graded by their architecture and proportions of solid and glandular areas, with tumours having less than 5% of solid growth as grade 1; 6-50% as grade 2 and more than 50% solid growth as grade 3. Grade 1 and 2 tumours are considered low grade and usually involve less than 50% of the myometrium, less than 10% lymph node metastasis and have an average 90% five-year survival rate (7).

Mucinous endometrial carcinomas show mucinous differentiation in more than 50% of the tumour. The architecture is glandular or villous and composed of columnar cells with minimal stratification. The mucin appears as intracytoplasmic basophilic secretory material. There is usually only mild nuclear atypia and low mitotic activity. These tumours are well differentiated and have a good prognosis (7).

Serous carcinomas are characterized by complex papillary architecture with diffuse marked nuclear pleomorphism. The cells have enlarged nuclei with scant cytoplasm, imparting a scalloped appearance to the luminal surface. There is usually extensive necrosis and mitotic activity with areas of psammomatous calcification and myometrial invasion. These are classical type II tumours. These tumours often present in post-menopausal women who are multiparous and are smokers. Immunohistochemical staining of serous tumours shows diffuse positive nuclear staining with p53 and patchy p16 expression and an absence of hormone receptors, such as oestrogen and progesterone

receptor, which can be used to differentiate it from papillary areas within an endometrioid adenocarcinoma. Wilms tumour 1 (WT1) immunohistochemical staining may be used to differentiate it from ovarian serous carcinoma, in which it is positive (7).

Clear cell carcinoma is a subtype of endometrial carcinoma that is composed of large cells with distinct cellular membranes that have large amounts of glycogen. The tumour displays tubulocystic, papillary or solid architectural patterns. Papillary projections and 'hobnailing' of tumour nuclei are similar to that seen in clear cell ovarian tumours. (7) 'Hobnailing' occurs when the nuclei of tumour cells are apically located and bulge into the luminal spaces of ducts.

Mixed epithelial and mesenchymal tumours include adenosarcomas and carcinosarcomas. Adenosarcomas have a benign or atypical epithelial component and a low grade malignant stromal component. These tumours are papillary to polypoid neoplasms that project into cystically dilated glandular lumina. The stroma is cellular and may show stromal overgrowth. There may be heterologous differentiation (into cartilage or skeletal muscle)(4). Carcinosarcomas are rare, biphasic tumours composed of high grade carcinomatous and stromal elements. These are also termed "Malignant Mixed Műllerian tumours" and may be associated with tamoxifen use and pelvic radiation. The two malignant components are usually sharply demarcated. The epithelial component can be endometrioid or serous. The malignant mesenchymal component is usually a high grade, non –specific sarcoma but may also show heterologous elements (including cartilage, skeletal muscle or bone). Deep myometrial and lymphovascular invasion is common(7).

Tumours that occur in younger, premenopausal women present at an earlier stage and are low grade. Conversely, tumours that present in post-menopausal females are usually of a high grade or serous carcinoma and present at a later stage (8).

The initial investigation includes a transvaginal ultrasound followed by an endometrial sample. Ultrasound thickness of greater than 4mm is considered worrisome and requires biopsy. If ultrasound is not available, an endometrial sample may be performed on its own (9). The diagnosis is made on a variety of preoperative biopsy methods, including hysteroscopy, Pipelle sampling and diagnostic dilatation and curettage (DD&C). In South Africa the Pipelle/ "Z-Sample" sample is most commonly used as it is the most easily accessible and economical method. It is performed on an outpatient basis, does not require general anaesthesia and is more comfortable for the patient. It has been demonstrated that this method can be as reasonably sensitive (84.2%) if used correctly (10).

Endometrial carcinoma may form broad based polypoid masses, or infiltrate diffusely into the myometrium. This may be missed on undirected biopsies. Hysteroscopy may be beneficial in these cases to direct biopsies more accurately(11).

The determination of histological subtype and grade in the biopsy specimen are important factors in predicting disease progression and outcome. These factors correlate with depth of myometrial invasion, lymph node involvement, surgical stage and survival. This in turn guides the extent of the surgical excision to be performed (12).

Tumour stage can generally only be finalized after hysterectomy as biopsies often do not allow for assessment of myometrial invasion. This will determine the need for adjunctive therapy. The plan of surgical management is therefore largely dependent on the histological subtype and grade of tumour determined on the biopsy. The biopsy specimen is often immediately fixed in formalin resulting in a better quality sample for assessment and immunohistochemical staining compared to the final hysterectomy specimen(13).

A meta-analysis by Clark *et al*. (14) showed an accuracy of up to 99% in the diagnosis of endometrial carcinoma, however this was variable between amongst the twelve studies

analysed. The diagnosis of benign diseases (including endometrial polyps) was found to be less accurate. In this study, diagnostic dilatation and curettage (DD&C) was used a reference standard. Hysteroscopy is now regarded as the new gold standard as it allows for guided and more accurate biopsies of focal lesions. A meta-analysis by van Hanegem *et al.* (15) however, showed a sensitivity of close to 100% for DD&C and 90% for hysteroscopic guided biopsy. The failure rate of endometrial sampling with the above methods was 11% (mostly due to cervical stenosis) and insufficient samples in 31% of cases. A diagnosis of atypical hyperplasia or carcinoma was found in 7% of these failed or insufficient cases, highlighting the need for repeat biopsies in these patients. A similar study by Moradan *et al*. (16) showed a relatively high sensitivity of 83.3% of DD&C for the diagnosis of endometrial pathology with a lower sensitivity in the detection of benign lesions such as polyps or hyperplasia (62%).

A study by Hartman *et al* (17) concluded that preoperative endometrial sampling was only a modest predictor of surgical pathology findings and may underestimate the risk of disease spread and recurrence.

For staging purposes, the depth of invasion into the myometrium is divided into more than or less than 50%. True myometrial extension should be differentiated from expansion of the endometrial-myometrial junction and from atypical or malignant changes involving pre-existing foci of adenomyosis(18).

Extension of tumour into the cervix occurs in 10% of cases (19). Lymphovascular invasion is the most important route of spread. In endometrioid endometrial carcinoma**,** this is via the pelvic and para-aortic lymph nodes and the ovaries. Nodal metastases are more common in high grade tumours, tumours that are large in size, deeply invasive or involve

the cervix(20). Serous carcinoma usually spreads via lymphatics. Peritoneal spread tends to occur early in disease and hence the tumour has a more aggressive behaviour (7).

The major genetic mutations that occur in endometrioid endometrial carcinomas include: microsatellite instability (28%), mutations in Phosphatase and tensin homolog (*PTEN*), Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (*PIK3CA*) gene, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene and the Beta catenin gene. The genetic mutations that characterize serous endometrial carcinomas are *TP53* (more than 90%) and heterozygosity loss. Many of these genes function as tumour suppressor genes and therefore loss of function mutations contributes to genomic instability. These genetic mutations may help in the diagnosis, classification and targeted therapy of endometrial carcinomas in the future (21).

Histological findings, including the grade and staging of endometrial carcinomas are essential predictors of disease outcome and lymph node involvement. Many gynaecological surgeons rely on the preoperative biopsy in determining management of patients with malignant disease (17).

With the socioeconomic transition that is occurring in many developing countries, including South Africa, it is expected that the prevalence of these risk factors and hence the prevalence of endometrial carcinoma will increase. There will therefore be an increased need for cost effective screening and accurate diagnostic procedures that can be used in resource limited settings. Wherever possible, it is important to accurately grade the preoperative biopsy in order to decrease the unnecessary complications of radical surgery, including, lymphoedema, loss of fertility and endogenous hormone production by the ovaries as well as extended surgical time and associated costs. (13) Limited data is available in South Africa regarding the accuracy of endometrial biopsies.

The aim of this study is to determine the concordance between endometrial biopsies and the hysterectomy specimens in the diagnosis of endometrial carcinoma.

2. **Objectives:**

- To determine the accuracy of preoperative endometrial biopsy specimens by comparing them to the diagnosis made on the final hysterectomy specimen.
- To determine the prevalence of different types of endometrial tumours seen in the Department of Anatomical Pathology, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
- To record patient demographics (age, parity, menopausal status) as well as surgical details (type of hysterectomy, duration between biopsy and surgery)

3. Materials and methods:

3.1 Study design:

The study will be a retrospective, cross sectional study of women who underwent a hysterectomy for a malignancy of the uterine corpus.

3.2. The site of study:

The Department of Anatomical Pathology of the University of the Witwatersrand/ National Health Laboratory Services.

3.3. The study time period

Applicable cases seen during a 3-year time period from January 2015 to December 2018. Cases will be selected consecutively from the most recent date.

3.4. Study sample size:

In order to generate a sample size that shows a statistically significant difference ($p \leq 0.05$) at 80% power, the sample was calculated using the equation:

$$N = 15.5 \times p.q \div d^2$$

Where p=3% (expected from previous data)

N= Number of cases; q=1-p and d is the difference between the expected and observed values.

$N= (15.5 \times 0.03 \times 0.97) \div (0.07)^2$

$N = 0.45105 \div 0.0036$

$N = 125.29$

Therefore, the desired sample size for statistical relevance is 126 cases.

3.5 Inclusion and Exclusion Criteria:

Inclusion criterion:

Female patients of all ages with a histologically confirmed carcinoma of the endometrium who have undergone a hysterectomy

Exclusion criteria:

- Reported cases of endometrial carcinoma where the slides and/or paraffin embedded tissue blocks cannot be found
- Incomplete or partially complete reports
- Hysterectomy specimens in which the entire tumour was autolyzed

3.6 Methods:

1. The NHLS database will be searched using a Systematized Nomenclature of Medicine (SNOMED) based search. This will be performed to retrieve *at least 126* cases of endometrial carcinomas for the period *January 2015- December 2018*.

   Diagnostic reports will be searched for "uterus" and the following terms:

   "malignant neoplasm"

   "carcinoma"

   "endometrioid carcinoma"

   "serous carcinoma"

"clear cell carcinoma"

"mucinous carcinoma"

"carcinosarcoma"

"adenosarcoma"

2. The stained slides of both the hysterectomy specimen as well as the preoperative biopsy will be retrieved from departmental archives. All pathology reports and slides will be reviewed by the pathologist (supervisor) and the principal investigator. Histology, grade and depth of myometrial invasion, cervical and lymphovascular and perineural invasion will be recorded. See Annexure A.
3. The preoperative endometrial samples will also be reviewed. Information will be collected regarding type and grade of tumour. This will be compared to the final diagnosis made after hysterectomy. See Annexure A.

4. Data analysis:

Inter observer variability will be determined using Kappa statistics for agreement of *histological type and grade* between preoperative and final pathology, with 95% confidence intervals. Conventional methods of interpreting kappa (K) values will be used with level of agreement categories of "poor/slight" (K 0.0–0.20), "fair" (K 0.21–0.40), "moderate" (K 0.41–0.60), "strong/substantial"(K 0.61–0.80), "almost perfect"(K 0.81–1.00) (22). The data will be expressed quantitatively as summary statistics and/or visually as graphs and/or tables. The distribution of data (including sensitivity, specificity, positive and negative predictive value as well as diagnostic accuracy) will be determined using the statistical programme, STATISTICA.

5. Funding:

The study will not require funding as it a retrospective study on procedures that have already been performed and with a final diagnosis.

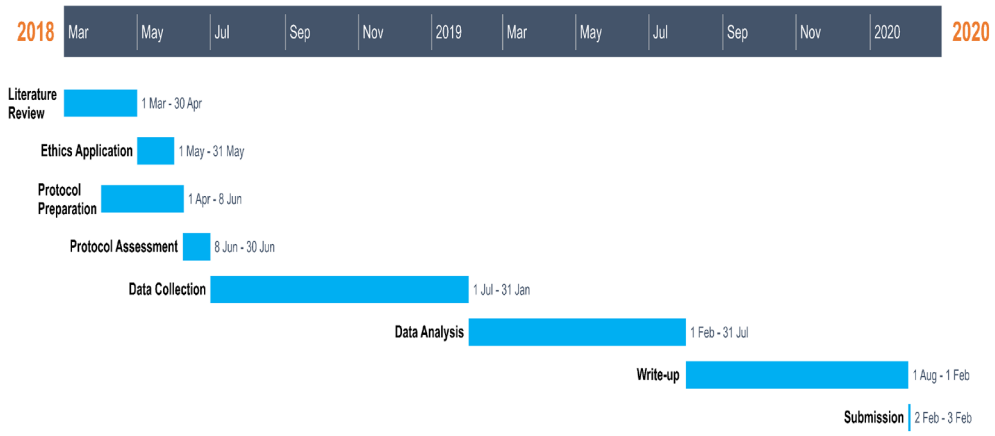
6. Ethics:

A project specific application to the Human Research Ethics Committee (Medical) and Faculty of Health sciences of the University of the Witwatersrand, Postgraduate office has been submitted *and approved (clearance certificate no. M180628).* There is currently blanket ethics approval (M1074) for use of archived departmental material.

The data sheet will be anonymous with only the accession number of the case being used for record purposes. There will be no personal information (such as name) on the data sheet. Patient reports and slides will be kept in a locked cupboard in the Department of Anatomical Pathology, Medical School, to which only the applicant and supervisor shall have access. The final submission will not have any personal patient information. Patient privacy will be maintained throughout the study.

This retrospective study will incur no additional cost to the patient or hospital. As this is a retrospective study, informed consent is not required.

7. Timeline:



8. Anticipated difficulties:

Obtaining all slides may not be possible due to lost slides. In this scenario, slides may be recut from the original wax tissue block.

Annexure A:

Data collection sheet

Case number			
Age			
Parity			
Menopausal status			
Duration between biopsy and hysterectomy			
Number of biopsies before hysterectomy			
Type of hysterectomy (radical, total, subtotal)			
Biopsy diagnosis: Benign Inadequate			
Malignant Histological type			
Grade 1/2/3			

Hysterectomy: Histological type			
Grade			
Depth of myometrial invasion			
Final staging			
Cervical stromal involvement			
Lymphovascular invasion			
Other (if applicable): *Immunohistochemistry :* *Quality of specimen:*			

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CLEARANCE CERTIFICATE NO. M180628

NAME: (Principal Investigator)	Dr Abdullah Ismail
DEPARTMENT:	Anatomical Pathology Charlotte Maxeke Johannesburg Academic Hospital National Health Laboratory Services
PROJECT TITLE:	A comparison of malignant histopathological diagnoses on uterine curettings and hysterectomy specimens
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Reubina Wadee
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/06/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

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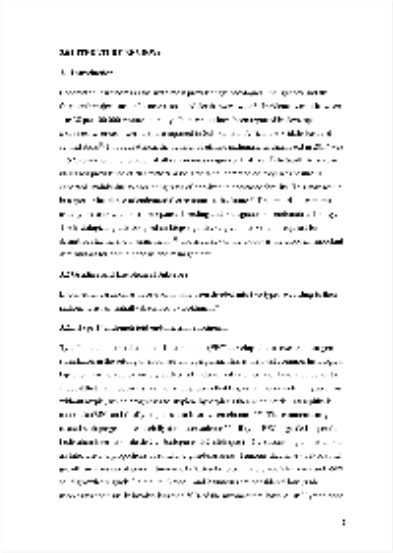

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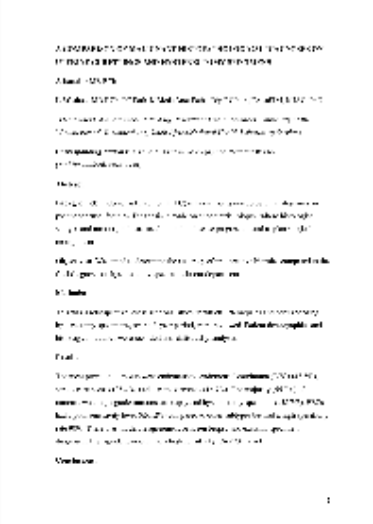

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