Clinical profile and management of women treated for endometrial carcinoma in Durban

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Declaration

This study represents original work by the author and has not been submitted in any form to another university. Where use was made of the work of others, it has been duly acknowledged in the text.

The research topic is titled **"Clinical profile and management of women treated for endometrial carcinoma in Durban".**

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Prof. J.S. Bagratee

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Glossary

IALCH	Inkosi Albert Luthuli Central Hospital
ICD	International Classification of Disease
HIV	Human Immunodeficiency Syndrome
HRT	Hormone Replacement Therapy
LGSIL	Low Grade Squamous Intraepithelial Lesion
HGSIL	High Grade Squamous Intraepithelial Lesion
HPV	Human Papilloma Virus
COC	Combined Oral Contraceptive
BMI	Body Mass Index
TAH	Total Abdominal Hysterectomy
TAH + BSO	Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy
VH	Vaginal Hysterectomy
LAVH	Laparoscopically Assisted Vaginal Hysterectomy
FIGO	International Federation of Gynaecology and Obstetrics
MMMT	Malignant Mixed Müllerian Tumour
MRI	Magnetic Resonance Imaging
SD	Standard Deviation
ASIR	Age standardised incidence ratios
PCOS	Polycystic ovarian syndrome
DD&C	Diagnostic dilatation and curettage
Pap	Papanicolaou
PR	Progesterone receptor
ER	Oestrogen receptor
GnRH	Gonadotropin receptor hormone

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Abstract

Background

Endometrial carcinoma is the second most common gynaecological cancer and the sixth most common cancer occurring in women. A significant number of women in South Africa are diagnosed with the disease each year. The National Cancer Registry of South Africa (2010) reported that 1 082 women were diagnosed with endometrial cancer. Endometrial cancer accounted for 3.64% of all cancers diagnosed in women compared to cervical cancer which accounted for 15.25% of all female cancers

Aim

To determine the clinical profile and management of women treated for endometrial carcinoma in Durban, South Africa.

Method

Retrospective chart review of women diagnosed with endometrial carcinoma over a 6-year period. Eligible women were identified from a clinical database (all the records in the study site). All relevant variables were recorded onto a structured data sheet which included race, age, age at menarche, age at menopause, obesity (BMI), parity, PCOS, hypertension, diabetes mellitus, HIV status, tamoxifen use, familial predisposition (Lynch syndrome), history of breast cancer, history of combined oral contraceptive use, postmenopausal bleeding, mode of histological diagnosis, FIGO staging, histological subtype, radiation therapy to the pelvis, management and postoperative complications. Data was electronically captured using MS Excel and imported into SPSS version 22 (SPSS Inc. Chicago) for analysis.

Results

Two hundred women during the study period of 6 years were diagnosed with endometrial carcinoma. The mean ± SD age at presentation of endometrial carcinoma was 63.8 ± 9.4. The main presenting complaint was postmenopausal bleeding (n = 187; 93.5%). Age and obesity were the most significant predisposing factors.

In our study 95 (47.5%) of endometrial carcinomas were diagnosed in Indian women and 92 (46%) in black women. One hundred and eighty seven (93.5%) of the patients were HIV negative. One hundred and eighty seven (93.5%) patients were postmenopausal. Thirty two (16%) patients were nulliparous. Hypertension was found in 108 (54%) patients and 52 (26%) presented with both hypertension and diabetes mellitus. One hundred and eighty seven (93%) patients diagnosed with endometrial carcinoma were above fifty years of age and only thirteen (7%) were below fifty years of age. The mean ± SD endometrial thickness was 22.1 ± 5.9mm. Eighty-eight (44%) patients with endometrial carcinoma had an abnormal Pap smear result; however none detected the presence of abnormal endometrial cells. The profile of women with endometrial carcinoma showed that 13 (6.5%) had a normal BMI,89 (44.5%) were overweight and 97 (48.5%) were obese.

In 193 (96.5%) women, endometrial cancer was diagnosed using a Pipelle biopsy, and 7 (3.5%) were diagnosed by DD&C. One hundred and forty seven (73.5%) endometrial carcinomas identified in our study were of the endometrioid subtype and the remaining 53 (26%) comprised serous carcinoma, clear cell carcinoma and carcinosarcoma. Eighty two (86%) Indian patients diagnosed with endometrial carcinoma presented with an endometrioid subtype, whereas the endometrioid subtype was observed in 54 (58.7%) black women. Twenty three (25%) black patients diagnosed with endometrial carcinoma had carcinosarcoma, whereas that was found in 7 (7.4%) Indian women.

Surgery was performed as the primary treatment in 171 (85.5%) patients. One hundred and fifty (88.3%) of the 171 patients received adjuvant therapy following surgery.There was a significant association between BMI (obese 31% vs. normal 3%) and perioperative complications ($p < 0.001$). Twenty (11.7%) patients had perioperative complications. Eight (4.7%) presented with wound haematomas and5 (2.9%) presented with wound sepsis.

All patients reviewed at the combined gynaecology / oncology clinic at IALCH are scheduled for routine follow up. It is unknown how many patients were lost to follow up. Twenty eight (14%) patients had recurrent malignancy. Carcinosarcoma (n = 5; 15.6%) and endometrioid endometrial carcinoma (n = 22; 15.0%) had the highest recurrence rate.

Conclusion

The results of the current study indicate that although endometrial carcinoma was more frequent among women who were older; especially after menopause, it may also occur in younger women in the premenopausal age group. Advancing age and obesity were the two important predisposing factors for endometrial carcinoma. In addition an increased BMI was associated with an increased proportion of post-operative complications.

In African women, 58% of women diagnosed with endometrial carcinoma had the endometrioid subtype and 25% had carcinosarcoma. In Indian women, 86% of women diagnosed with endometrial carcinoma had the endometrioid subtype and 7% had carcinosarcoma.

CHAPTER 1:

INTRODUCTION & LITERATURE SURVEY

1.1. Background

Endometrial carcinoma is a gynaecological malignancy that arises from the endometrium. Worldwide it is the second most common gynaecological malignancy. (1)The South African National Cancer Registry (2010) reported that endometrial carcinoma was the second most common gynaecological cancer and the sixth most common cancer occurring in women. (10)

1.2. Incidence

Incidences, however, show a wide variation among different regions in industrialised countries. In industrialised nations the overall lifetime risk of endometrial carcinoma is 1.6%. (2) This is in comparison to a 0.6% overall incidence seen in poorer socio-economic countries. (2) In the United States of America and the United Kingdom, it was found to be the fourth most common cancer in women. The lifetime risk was found to be 3.9 and 2 – 3%, respectively. (3) Advancing age was identified as a risk factor for the development of endometrial cancer. (4,5) Most women diagnosed with endometrial carcinoma are postmenopausal. However, 25% are premenopausal and 4% are less than 40 years of age at the time of diagnosis. (6) Women older than 70 years have a 1 in 81 risk for developing endometrial carcinoma compared to the risk of 1 in 1 423 found in women younger than 40 years of age. (5, 7) In a rare case report a 13-year-old Korean girl was diagnosed with grade II endometrial adenocarcinoma after she presented with abnormal uterine bleeding. (8)

There has been an international increase in the incidence of endometrial carcinoma attributed both to the increase in the ageing female population and the rise in obesity. (9) In South Africa, uterine carcinoma is the 3rd most common gynaecological carcinoma and is ranked 3rd in Asians (7.1%), 5th in Africans (4.4%), 6th in Coloureds (3.48%) and 7th among Caucasian (2.1%) women. (10) The lifetime risk of endometrial carcinoma among the subpopulations in South Africa is shown in Table 1.

Table 1: Lifetime risk of endometrial carcinoma among the different racial groups in South Africa (2010) (10)

Racial groups	Number of cases	Lifetime risk
Asian	68	1:87
Black	691	1:180
Coloured	108	1:133
White	215	1:144

A white female in the USA has a lifetime risk of 2.88% for endometrial cancer with a mortality rate of 3.9 / 100 000, compared to a black female who has a 1.69% lifetime risk and a mortality rate of 7.2 per 100 000. (11)

Among the South African population the age standardised incidence ratios (ASIR) of endometrial carcinoma are 4.26, 4.86, 6.31, and 6.64 per 100 000 population in Blacks, Asians, Whites and Coloureds, respectively. (12) In the United States, the figures for White, Black, Asian and Hispanic women were 24.8, 20.9, 18.2 and 15.9 per 100 000 population, respectively. (13) Similarly in the UK the figures for White, Asian and Black women were 16.9 - 17.7, 10.7 - 18.0 and 13.7 - 23.6 per 100 000 population, respectively. (14) Table 2 lists the age standardised incidence ratios of three different countries.

Table 2: Age standardised incidence ratios (ASIR) of endometrial carcinoma in South African, American and United Kingdom subpopulations

Country	ASIR
South Africa	
Blacks	4.26 / 100 000
Asian	4.86 / 100 000
White	6.31 / 100 000
Coloured	6.64 / 100 000
United States of America	
White	24.8 / 100 000
Black Americans	20.9 / 100 000
Asian	18.2 / 100 000
Hispanic	15.9 / 100 000
United Kingdom	
White	16.9 – 17.7 / 100 000
Asian	10.7 – 18.0 / 100 000
Black	13.7 – 23.6 / 100 000

Uterine cancer may present with abnormal uterine bleeding or an abnormal vaginal discharge, and pelvic pain or pressure. (15) The commonest clinical presentation is that of abnormal uterine bleeding. (16) This refers to either intermenstrual or heavy menstrual bleeding. (16) Any amount of vaginal bleeding is abnormal in the postmenopausal female and requires investigation. (16, 17) Postmenopausal bleeding refers to any vaginal bleeding (even a single drop) that occurs more than 12 months after the cessation of menses. (16, 18, 19)

Diagnostic evaluation for endometrial carcinoma may be recommended in a woman who presents with abnormal uterine bleeding. Methods of endometrial sampling include an endometrial biopsy and hysteroscopy. (18, 20) These investigations involve taking a sample of the endometrium, which is then examined for the presence of abnormal or dysplastic cells. A transvaginal ultrasound is an essential component of the evaluation in a woman presenting with abnormal uterine bleeding.

Endometrial cancer is staged using the FIGO system once a tissue diagnosis has been made. (16, 21–23) The basis for staging includes the depth of uterine muscle infiltration by the cancer, and spread to other organs. (21) This can be determined on a comprehensive physical examination and supportive diagnostic imaging. (16) Stages range from I where the malignancy has not invaded beyond the uterine lining, to stage IV where it has spread to distant organs. (16) Lower stage endometrial carcinomas are usually considered to be less aggressive and require less treatment compared to higher grade malignancies. (16)

A laparotomy is usually performed as part of staging endometrial carcinomas. A TAH with BSO, para-aortic and pelvic lymphadenectomy and peritoneal washings offers a therapeutic benefit in addition to aiding the staging of the disease. (16, 23) During laparotomy the para-aortic and pelvic lymph nodes are examined and a lymphadenectomy is performed, as the lymph nodes is one the first places endometrial cancer spreads to. (16) Peritoneal washings and any other abnormal pelvic or abdominal tissue are collected for cytological and histological evaluation. (16) Cytoreductive surgery may be performed if there is evidence of metastases. (23)

A risk assessment is performed to aid the planning of treatment of endometrial carcinoma. This assessment is based on the likelihood of recurrence of the malignancy. The following factors are taken into consideration: (16)

- The stage of the cancer, as determined at laparotomy
- The grade of the tumour on histology
- The histological subtype of the tumour

1.3 Staging and classification of endometrial carcinoma

Endometrial carcinoma is surgically staged according to the Joint International Federation of Gynaecology and Obstetrics (FIGO) / TNM classification system(2009): (21)

FIGO ENDOMETRIAL CANCER STAGING CRITERIA (2009)

- IA: Tumour confined to the uterus with no or < 50% myometrial invasion
- IB: Tumour confined to the uterus with ≥ 50% of the myometrium
- II: Cervical stromal invasion but not beyond the uterus
- IIIA: Tumour invades the serosa or adnexa
- IIIB: Vaginal and / or parametrial involvement
- IIIC1: Pelvic node involvement
- IIIC2: Para-aortic lymph node involvement
- IVA : Tumour invasion to bladder and / or bowel mucosa
- IVB : Distant metastases – including abdominal metastases and / or inguinal lymph nodes

FIGO ENDOMETRIAL CANCER STAGING CRITERIA (1988)

- IA: Tumour limited to the endometrium
- IB: Invasion to less than 50% of the myometrium
- IC: Invasion to more than 50% of the myometrium
- IIA: Endocervical glandular involvement only
- IIB: Cervical stromal invasion
- IIIA: Adnexal or serosal involvement or positive peritoneal cytology
- IIIB: Vaginal metastases
- IIIC: Metastases to pelvic or para-aortic lymph nodes
- IVA: Bowel or bladder mucosal invasion
- IVB: Distant metastases – includes omental and inguinal metastases

1.3.1 Histopathological grading of endometrial carcinoma (24)

- Grade 1: Adenocarcinoma having 5% or less non-squamous or non-solid growth
- Grade 2: Adenocarcinoma having 6 - 50% of solid growth
- Grade 3: Adenocarcinoma having more than 50% of solid growth

1.3.2 Classification and histopathological features of endometrial carcinoma

Endometrial carcinoma develops from normal epithelium and is preceded by pre-carcinomatous hyperplastic cells with mild to moderate architectural abnormality. The histological presentation of this pre-carcinomatous hyperplastic stage is often typical. Endometrial hyperplasia was previously classified into 4 subtypes: (24–26)

(1) Simple hyperplasia without atypical cells
(2) Simple hyperplasia with atypical cells
(3) Complex hyperplasia without atypical cells
(4) Complex hyperplasia with atypical cells

Normally simple and complex hyperplasia's are not significant pre-carcinomatous lesions and less than 10% progress to invasive carcinoma. However, when atypical cells are present the risk increases to 10 – 20%. (27) The progression to carcinoma occurs in 1% and 3% of patients with simple and complex hyperplasia without atypical cells, respectively, compared to 8% and 29% of patients with simple and complex hyperplasia with atypical cells. (28) Within ten years, 8 – 30% of patients with atypical endometrial hyperplasia's develop into endometrial cancer, whereas only 1 – 3% of non-atypical hyperplasia undergoes this progression. (28, 29)

In 2014 the WHO issued a simplified classification as the previous and parallel classifications caused confusion among clinicians and led to incorrect treatment. (26) The new classification only recognises two categories: (26)

- Hyperplasia without atypia
- Atypical hyperplasia / endometrioid intraepithelial hyperplasia

The endometrial intraepithelial neoplasia (EIN) is a system used to classify precancerous lesions of the endometrium. (30) It shows high interobserver reproducibility. Epithelial crowding in premalignant lesions displaces endometrial stroma until it reaches a volume of less than 50% of the total tissue. Stromal volume can be measured using a D-score. (30–32)

The majority of the malignant tumours of the endometrium are well-differentiated adenocarcinomas. These include:(33)

- **Endometrioid** (75%)
    - Ciliated adenocarcinoma
    - Secretory adenocarcinoma
    - Papillary and villoglandular adenocarcinomas
    - Adenocarcinoma with squamous differentiation
        - Adenoacanthoma
        - Adenosquamous cells
- **Mixed**, defined as two carcinomatous cell types, with the smaller component making up at least 10% of the total (10%)
- **Uterine papillary serous** (<10%)
- **Clear cell**(4%)
- **Carcinosarcoma** (3%)
- **Mucinous** (1%)
- **Squamous cell** (<1%)
- **Undifferentiated** (<1%)

Endometrial carcinoma invades the myometrium at an early stage and remains confined to the uterus until the later stages of the disease. (34) Based on histology and clinical assessment there are two main types of endometrial adenocarcinoma.

1.4 Two main types of endometrial adenocarcinoma

Type I (endometrioid adenocarcinoma of the endometrial epithelium), is a low grade adenocarcinoma confined to the uterus with minimal invasion, is oestrogen dependant, and it occurs in younger or perimenopausal women. (5) Approximately 85% of endometrial carcinomas are type I. (5) They occur in women with an increased BMI and is usually preceded by complex atypical hyperplasia. (5, 35, 36) Owing to their early diagnosis secondary to postmenopausal bleeding and having more benign histological features, they have a good prognosis.

Type II (serous or clear cell) endometrial tumours are aggressive, non-oestrogen dependent and non-endometrioid. (5) They typically occur in thin, older patients who have an atrophic endometrium. (5, 35, 37) They typically present with high-grade serous or clear cell histological subtypes and are associated with early metastases. (5, 8, 35) Fifty percent of patients presenting with endometrial cancer relapse, occur in patients diagnosed with type II tumours. (5, 38) Type II endometrial carcinomas develop in older patients, are not hormone-dependent and are responsible for most of the recurrences and deaths associated with endometrial carcinoma. (5)

The two tumour types display distinct molecular variation. Molecular characteristics of type I endometrial tumours include K-RAS, PTEN, microsatellite instability (MSI),β-catenin mutations and large quantities of progesterone receptors. (5, 35) Type II endometrial tumours show p53 mutations and HER2 / neu amplification. (5, 38, 39) Table 3 summarises the differences between type I and type II endometrial carcinomas.

Table 3: Differences between type I and type II endometrial carcinomas

Difference	Type I	Type II
• Patient	< 65 years, obese, perimenopausal	Older females (> 65 years)
• Grade	Low-grade, benign histological features	High-grade, complex histology
• Histology	Endometrioid	Serous or clear cell
• Hormone dependency	Oestrogen dependent	Non-oestrogen dependent
• Tumour development	Hyperplastic epithelium	Atrophic epithelium
• Stage at diagnosis	I or II	III or IV
• Genetic factors	PTEN, MSI, β-catenin	HER2 / neu, p53
• Clinical course	Indolent (good prognosis)	Aggressive (poor prognosis)

Although endometrioid adenocarcinoma originates from the atypical hyperplastic cells, some of these carcinomas arise from an atrophic endometrium. Uterine serous papillary carcinoma is an uncommon form of endometrial cancer. It does not develop from endometrial hyperplasia and is not hormone sensitive. It does however arise in the background of endometrial atrophy.(34, 40)

1.5 Predisposing factors for endometrial carcinoma

The following factors may increase a woman's risk of developing uterine carcinoma: obesity, diabetes, hypertension, unrestricted oestrogen, and tamoxifen use for > 5 years. The risk of unrestricted oestrogen is potentially associated with obesity, polycystic ovarian syndrome, nulliparity, late menopause, oestrogen-producing tumours, anovulation and oestrogen monotherapy. (23, 41)

Inherited factors contribute to endometrial cancer in as many as 10% of cases. Approximately half of these cases occur in families with a hereditary predisposition for nonpolyposis colorectal carcinoma (Lynch syndrome)

Heredity factors contribute to endometrial carcinoma in as many as 10% of cases, with approximately half of these cases occurring in families with hereditary nonpolyposis colorectal carcinoma (Lynch syndrome) who have a marked increase in risk of endometrial cancer compared to that of the general population. (23, 42)

1.5.1 Age

Endometrial cancer is more common in older, peri-menopausal or postmenopausal women, with mean age at diagnosis being in the early 60s. (5, 43) Only 25% of cases occur in premenopausal women, and only 5 – 10% of these women are less than 40 years of age. (5, 44) There is only a 0.05% overall probability of developing endometrial cancer between birth and the age of 39 years. (5, 45) Women younger than 50 years with endometrial cancer often have associated comorbidities including obesity, nulliparity, hypertension and diabetes mellitus. (46)

1.5.2 Exposure to oestrogen

Risk is increased with increased duration of use and dose.

1.5.2.1 Exogenous oestrogen

- Hormone replacement without progestin
- Tamoxifen use for breast cancer

Oestrogen therapy in the postmenopausal woman offers a number of short- and long-term benefits as it improves hot flushes, vaginal dryness and helps to maintain bone mineral density. (46)Unopposed oestrogen use increases a woman's risk for both endometrial hyperplasia and carcinoma. (46–48) Five years of oral contraceptive use may halve the risk of developing endometrial carcinoma. (5, 49) The concomitant administration of progestins significantly decreases the risk of developing endometrial hyperplasia and carcinoma. (46, 50–52) The risk of developing endometrial cancer from oestrogen therapy is dose dependent. (5, 53, 54) Both case control and prospective studies demonstrated an increased

incidence of endometrial carcinoma associated with oestrogen therapy, the relative risk ranging from 3.1 to 15. (46, 55, 56)

1.5.2.2 Endogenous oestrogen

- Obesity (overweight and obesity)
- Polycystic ovarian syndrome
- Oligoamenorrhoea
- Infertility
- Nulliparity
- Early menarche (< 12 years) / Late menopause (> 52 years)
- Oestrogen-producing tumours
- Comorbid disease (diabetes mellitus and hypertension)
- Genetic factors

The risk of developing endometrial carcinoma from endogenous oestrogen is related to the conversion of adrenal precursors to oestrone and oestradiol by adipose cells in the body. (46) A postmenopausal woman's risk of developing endometrial carcinoma is correlated with both higher circulating oestrogen and androgen levels, and lower sex hormone binding globulin levels. (46, 62– 66)

1.5.3 Tamoxifen use

Tamoxifen is a competitive inhibitor of oestrogen. (46) It binds to oestrogen receptors. It is a weak oestrogen, as it only has partial agonist activity. (46) It suppresses the growth of breast tissue but stimulates the endometrial lining. (46, 57) The risk of developing endometrial carcinoma from tamoxifen increases not only with a longer duration of use, but also with a higher cumulative dose. (5, 58, 59) Tamoxifen use has also been associated with benign endometrial pathology. (5, 60, 61)

1.5.4 Obesity

It is estimated that obesity increases the risk for endometrial cancer by 300 – 400%. (67) While overweight women have double the risk of developing endometrial cancer, obese women have four to five times the risk compared to normal weight women. (5, 68)

Women who have a BMI of > 32kg/ m^2 are four times more likely to develop endometrial cancer when compared to women with a BMI < 23kg/m^2, while obese women (BMI > 35kg/m^2) have six times the risk. (5, 69) For each increase of 5kg/m^2 in BMI, the risk of developing endometrial cancer is significantly increased. (5, 70) A higher BMI is also a risk factor for endometrial carcinoma in women under 45 years of age. (46, 71)

It is postulated that the peripheral conversion of androstenedione to oestrone and the aromatisation of androgens to oestradiol in the adipose tissue of overweight and obese women forms the basis for an increased risk of developing endometrial cancer, as these women have high levels of endogenous oestrogen. (46) Other postulated mechanisms include lower circulating levels of SHBG, alterations in the concentration of insulin like growth factor, and insulin resistance. (46, 72, 73)

1.5.5 Chronic anovulation (PCOS)

A recent case control study demonstrated that women under 50 years of age with PCOS have a four times higher risk of developing endometrial cancer. (9, 75) Constant oestrogenic stimulation of the endometrium in women with PCOS may lead to endometrial hyperplasia or endometrial carcinoma. (42, 46, 70) Endometrial carcinoma is associated with PCOS in the majority of young patients with up to 30% having concomitant PCOS. (43, 46, 76)

1.5.6 Nulliparity

The risk of endometrial cancer is inversely related to parity (46, 77–79) as nulliparous women have a 2 to 3 times higher risk of endometrial cancer. (46, 52) Nulliparity, however, is not an independent risk factor and the association most likely lies in the high number of anovulatory menstrual cycles in sub-fertile or infertile women. (46) Each child decreases a woman's risk of endometrial cancer. (80)

1.5.7 Early menarche and late menopause

Early menarche (younger than 12years) and late menopause (older than 55 years) are risk factors for endometrial cancer, although late menopause is a less consistent risk. (46, 69, 78, 81, 82) The underlying mechanism is thought to be prolonged oestrogen stimulation in the absence of protection by progesterone. (46)

1.5.8 Oestrogen-producing tumours

About 6 - 10% of patients with oestrogen-producing tumours will develop endometrial cancer. (5, 83)

1.5.9 Breast cancer

Partly because of common risk factors including obesity and nulliparity, a woman with a personal history of breast cancer is at a higher (2 to 3 fold) risk for developing endometrial cancer. (46) It is unclear whether the BRCA 1 gene has a role in the development of endometrial cancer. (46, 84, 85) Some studies suggest that only BRCA 1 carriers using tamoxifen have a higher risk of endometrial cancer. (86)

Postmenopausal patients receiving tamoxifen therapy are at a higher risk of developing endometrial carcinoma when compared to premenopausal women. (87–89)Breast cancer patients receiving adjuvant tamoxifen treatment have a 4 to 14 fold higher risk of developing endometrial carcinoma compared to healthy women who do not use tamoxifen. (46, 57, 90, 91) A prospective study by Cohen et.al found that symptomatic tamoxifen-treated breast cancer patients had a 22% incidence of endometrial carcinoma compared to a 1% incidence in asymptomatic tamoxifen-treated patients. (91, 92)

A large meta-analysis that included more than 20 000 women with breast cancer who were treated with tamoxifen for > 5 years found that these patients had a higher risk (rate ratio 2.40) of developing endometrial cancer, compared to women who did not receive tamoxifen. The risk, however, was only found to be significant in patients older than 55 years. (87, 89)

In patients on tamoxifen endometrial surveillance may be done with transvaginal ultrasound and regular endometrial sampling. (93) However, ACOG does not recommend routine endometrial surveillance in women taking tamoxifen unless the patient is symptomatic. (87, 94)

1.5.10 Diabetes mellitus and hypertension

Women who suffer from diabetes mellitus and / or hypertension have an increased risk of developing endometrial cancer. (5, 67, 95) Type 2 diabetes mellitus is a risk factor for endometrial carcinoma, even when adjusted for confounding factors such as obesity, and it confers a higher risk than type 1 diabetes mellitus. (5, 52, 96, 97)Diets high in carbohydrates are associated with hyperinsulinemia, insulin resistance and elevated levels of insulin like growth factor, all of which may contribute to endometrial proliferation and subsequent endometrial cancer. (98, 99)

1.5.11 Family predisposition and genetics

A family history confers a higher risk of endometrial cancer. (33) It has been suggested that there is a tendency toward isolated endometrial cancer in women with a first degree family history, but no consistent causative gene could be identified to date. (46, 100) Lynch syndrome is a familial condition associated with endometrial carcinoma, conferring a lifetime risk of 27 – 71% compared to 3% in the general female population. (9, 46)

1.6 Protective factors against endometrial carcinoma

- Combined oral contraceptives
- Parity
- Physical activity
- Lactation
- Smoking

1.6.1 Combined oral contraceptives

Combined oral contraceptives decrease the risk of endometrial cancer more, the longer they are used: 56% after 4 years, 67% after 8 years, and 72% after 12 years. (102, 103) This protective benefit lasts up to 15 years after cessation of COCs. (102, 103)

The protective mechanism of COCs is most likely related to the progestin component, as it suppresses endometrial proliferation. (46) A woman who has used COCs at some point in her life has a lower (0.5) relative risk of endometrial carcinoma. This protection occurs if a woman used COCs for at least 12 months, and is most noticeable in nulliparous women. (101)

1.6.2 Parity

Grand multiparity is a protective factor against endometrial cancer. Having one child decreases the individuals risk by 35%. (46)

1.6.3 Physical activity

It is unclear whether occupational or recreational physical activity offers protection against endometrial carcinoma. (101), (108–111) Risk reduction may be due to the associated decrease in obesity, favourable immune system changes and endogenous sexual and metabolic hormone levels and growth factor. (46, 112)

Approximately 50% of uterine carcinomas occur in women with these particular risk factors. Interestingly risk factors such as obesity, menstrual irregularities and nulliparity / infertility seem to be predominant in women younger than 40 years compared to older women where factors like hypertension and diabetes seem to be more common.

1.6.4 Lactation

Breastfeeding for more than 18 months may decrease the risk of endometrial cancer by up to 23%.

1.6.5 Smoking

There is an inverse relationship between cigarette smoking and endometrial cancer with a relative risk of 0.5%. (5, 69, 104–107) The effect is related to weight, as heavier women have the greatest risk reduction. (101)

1.7 Phenotypic characteristics

The existence of two pathogenic types of endometrial cancer, based on phenotypic characteristics, has been established. (101) These characteristics include the following:

Type I:

- Obesity
- Hyperlipidemia
- Signs of hyperestrogenism
- History of uterine bleeding
- Infertility
- Late onset of menopause
- Hyperplasia of the ovary and the endometrium
- Nulliparity

These patients tend to have well differentiated, superficially invasive endometrial cancer which is sensitive to progesterone. They tend to have a favourable prognosis, and extrauterine disease is uncommon. (101)

Type II:

None of the above characteristics are present in these women. Tumours are poorly differentiated, associated with deep myometrial invasion, have a high rate of nodal and distant metastases, have a decreased sensitivity toprogestins, and have a poor prognosis.

1.8 Methods of evaluating the endometrium

Evaluation of the endometrium is an important component in the diagnostic evaluation of women suspected of having endometrial cancer or in women where a premalignant endometrial lesion is suspected.

Evaluation methods are classified as either invasive or non-invasive. An endometrial biopsy or dilatation and curettage is commonly performed to diagnose endometrial cancer by obtaining a tissue sample for histology. (103)

1.8.1 Dilation and curettage

Dilation and curettage is used less frequently than endometrial biopsy, but it is still the gold standard for evaluation of the endometrium in the following clinical circumstances (113):

- When a patient is unable to tolerate an endometrial biopsy (e.g. due to excessive anxiety or pain)
- After a non-diagnostic office biopsy in women with an increased risk of endometrial carcinoma
- Following benign histology from an endometrial biopsy in a woman with persistent or recurrent abnormal uterine bleeding
- When there is insufficient tissue for adequate analysis following an office biopsy
- When cervical stenosis prevents a successful endometrial biopsy

Disadvantages of Dilatation and Curettage

- The entire endometrial cavity is not sampled. Only 60% of the endometrial cavity is sampled (113–115)
- The fractional curettage used to determine cervical involvement is inaccurate as it has significant false positive and false negative rates (67, 113, 116)

1.8.2 Endometrial biopsy

The Pipelle is the most extensively used device for endometrial sampling as it compares favourably to, and offers many advantages over standard dilation and curettage, and it has an excellent correlation for diagnosing endometrial carcinoma. (113, 117–119)

Advantages

- Less traumatic than hysteroscopy or dilatation and curettage
- Little or no anaesthesia needed
- Rapid, easy and relatively cheap method to diagnose endometrial carcinoma. However, it has limitations in that it might be inaccurate in diagnosing the true tumour grade in the uterus (120)

Thirty percent of (preoperative) grade I tumours are upgraded to a higher grade upon examining the postoperative sample. (121) Upgrading, however, is less likely to occur after dilation and curettage than Pipelle biopsy. (119) Renaud and Le found that only 8.7% of tumours diagnosed by dilation and curettage were upgraded, while 17.4% diagnosed via endometrial biopsy were upgraded. (113)

1.8.3 Hysteroscopy

Hysteroscopy is primarily used for the detection of polyps and other endometrial lesions in patients with persistent or recurrent abnormal uterine bleeding with benign endometrial sampling or deficient sampling by dilation and curettage or endometrial biopsy, as this method allows for direct visualisation of the endocervical canal and the endometrial cavity. (122) A number of studies have demonstrated that hysteroscopy can assist in the detection of focal lesions of the endometrial lining which may not be detected by dilation and curettage alone. (123–125)

Disadvantages

- Expensive (113)
- Only the gross anatomy of the endometrium is evaluated, which is often not indicative of cancer. It is rarely used, unless in circumstances where an endometrial biopsy is obtained(9, 103, 113)

1.8.4 Transvaginal ultrasound

Transvaginal ultrasound is widely used to evaluate endometrial thickness in patients presenting with postmenopausal bleeding. (126)It is a non-invasive method used to evaluate for endometrial hyperplasia or cancer in women with postmenopausal bleeding if the endometrium is homogenous, and is increasingly used to assist in the diagnosis of endometrial carcinoma. (9, 127)

An endometrial thickness of < 5mm is associated with a low risk of endometrial cancer. The ratio of malignant to benign disease increases as the endometrial thickness approaches 20mm. The sensitivity and specificity of transvaginal ultrasound for the detection of endometrial carcinoma at a threshold of 5mm thickness were 96% and 61%, respectively. (128) As a result of there being no standard threshold for endometrial thickness in premenopausal women, the role of transvaginal ultrasound in diagnosing endometrial cancer has not been established.

Transvaginal ultrasound is not a useful screening tool for excluding endometrial hyperplasia or cancer in patients on oestrogen therapy, irrespective of whether it is unopposed, or given with cyclic progesterone. Women receiving tamoxifen therapy, both for the prevention and treatment of breast cancer, commonly have thickened endometrial stripes. There is no well-defined cut off for normal vs. pathological endometrial thickness in this category of patients.

The criteria for a thickened endometrium necessitating intervention in postmenopausal women without any uterine bleeding have not been established. It is recommended that the clinician perform sampling of the endometrium in postmenopausal women without any uterine bleeding where the endometrial thickness is greater than 11mm. (129)

In asymptomatic premenopausal women endometrial thickening alone is not a justifiable indication for biopsy and endometrial sampling. Endometrial evaluation is based on a combination of factors which includes cervical cytology results showing glandular abnormalities or endometrial cells.

A number of studies reported that endometrial thickness ≤ 4 – 5mm in patients with postmenopausal bleeding reliably excluded endometrial cancer. (118, 130–132) Several

studies, however, found that endometrial cancer may occur even when the endometrial thickness on transvaginal ultrasound measures < 5mm. (126, 133–135)

Transvaginal ultrasound as an isolated screening test is inconclusive, and must be combined with another method, e.g. endometrial biopsy. (103)

Endometrial thickness measurements in postmenopausal bleeding in different conditions

- **History of postmenopausal bleeding (and not on HRT / tamoxifen):**
    - Suggested upper limit of normal is < 5mm (103, 128, 131, 132)
    - Risk of carcinoma (± 7%) if endometrium is > 5mm and 0.07% if endometrium is < 5mm (136)

- **No history of postmenopausal bleeding (and not on HRT / tamoxifen):**
    - An acceptable range of endometrial thickness is less well established in this group; cut-off values of 8 or 11mm have been suggested. (129)

- **On hormonal therapy:** upper limit is 8 - 15mm (137)
- **On tamoxifen:**< 6mm (138) (about 50% of those receiving tamoxifen have been reported to have a thickness of > 8 mm (139)

Endometrial thickness measurement in a patient taking tamoxifen

ACOG recommendations for endometrial cancer surveillance in women taking tamoxifen are(140):

- Postmenopausal women without postmenopausal bleeding should not undergo routine ultrasound examination or endometrial biopsy
- Endometrial evaluation, including biopsy, should be performed in patients presenting with abnormal uterine bleeding
- The following investigations are indicated in a premenopausal woman taking tamoxifen and presenting with abnormal uterine bleeding: hysteroscopy, hysterosonography, and biopsy if the aetiology remains unclear

- Tamoxifen leads to endometrial thickening in the absence of malignancy as it causes enlargement of subendometrial glands. Endometrial thickening alone should not prompt evaluation in a patient taking tamoxifen.

Asymptomatic women with endometrial fluid on ultrasound

The incidental finding of endometrial fluid in asymptomatic women with an endometrial thickness of < 3mm is unlikely due to endometrial hyperplasia or malignancy. A biopsy is indicated if the endometrial thickness is > 3mm as these women have an increased risk of endometrial malignancy. (136, 141)

Limitations

A reliable transvaginal ultrasound evaluation of endometrial thickness and texture may be hampered by an axial uterus, marked obesity, coexisting myomas and previous uterine surgery. (128, 142)

If a thin, distinct endometrial stripe in a bleeding, postmenopausal woman cannot be identified, an alternative method must be used. It is important to exclude endometrial fluid, if present, when measuring endometrial thickness. (128)

1.8.5 Other imaging studies

Imaging studies are discussed in more detail under the heading of 'Pre-treatment evaluation'.

1.8.6 Infusion sonohysterography

This technique is useful for better visualisation of anomalies and irregularities of the endometrial cavity. Liquid media is injected into the uterus prior to ultrasound examination. This procedure may be more uncomfortable but is usually well tolerated (Goldstein, 2011).

1.9 Pre-treatment evaluation

A comprehensive pelvic and general physical examination is required prior to commencing treatment for endometrial cancer. Clinical findings that should be noted include: Mobility and size of the uterus, presence of adnexal masses or ascites, and palpation for enlarged / pathological lymph nodes. (143, 193) Laboratory studies should be guided by the planned treatment modality, suspicion of metastases and patient comorbidities. Cervical cancer screening should be performed.(143)

1.9.1 Tumour markers

Serum CA – 125 may be a clinically useful marker to predict extra uterine spread of endometrial cancer. (143)

Preoperative raised CA – 125 levels have been associated with higher staged disease, presence of a serous component, and myometrial invasion. (194)One retrospective study found that a CA – 125 value of > 40units/ml has a 78% sensitivity and 81% specificity for nodal metastases. (143, 195)

An optimal threshold value has not been established. (143, 196–200) Serum CA – 125 levels are usually higher in premenopausal than postmenopausal women. (143)

1.9.2 Imaging studies

Special pelvic and / or abdominal imaging is unnecessary in most patients as endometrial carcinoma is a surgically staged malignancy. (21, 24, 143)

Compared to non-contrast enhanced MRI, CT, PET and ultrasound, contast enhanced MRI is the superior modality for detection of myometrial or cervical invasion, or lymph node spread. (143, 201–203) Studies have reported the sensitivity of contrast-enhanced MRI to detect myometrial invasion to be around 80 – 90%. (14, 143) Its sensitivity for cervical invasion is, however, more inconsistent ranging from 56 to 100%. As such a negative study cannot conclusively rule out local infiltration. (143)

Preoperative staging should include a chest X Ray and ultrasound of the abdomen to exclude lung and liver metastases, respectively. (93)

Some authors are of the opinion that MRI should be standard practice in well-resourced settings, as part of the preoperative workup. (93)

1.10 Management of women with endometrial carcinoma

Surgery is the primary treatment modality for early stage endometrial cancer, followed by adjuvant therapy in selected cases. This includes radiation therapy with or without chemotherapy, based on stratification of patients into categories depending on their future recurrence risk.

1.10.1 Surgical management

Surgery alone may be curative in patients with low risk disease i.e. endometrioid histology, grade 1 or 2, confined to the endometrium and there are no risk factors for persistence or recurrence. (143)

Total extra fascial hysterectomy with BSO, and aortic and pelvic lymphadenectomy has been the standard approach in patients who are medically fit for surgery and do not have obvious extrauterine disease. (21, 143) In addition, a complete staging laparotomy includes biopsies of any suspected metastases. Cytoreduction is done if there is intraoperative evidence of metastases.(143)The intraoperative assessment of lymph nodes is controversial and discussed in more detail below. At a minimum pelvic and para-aortic lymph nodes need to be palpated and enlarged or suspicious nodes excised. (143, 144) Gross intraoperative inspection of the uterine specimen by a pathologist to determine the depth of myometrial invasion has a 75% sensitivity and 92% specificity. (143, 145) The value of intraoperative frozen section is questionable. (146–149) Peritoneal fluid collection is not required in the 2009 FIGO staging. (24)

Laparoscopic, vaginal and robot assisted procedures are now also possible. (143)

Laparotomy vs. laparoscopy

Laparoscopy for the staging and treatment of endometrial carcinoma is a feasible and safe surgical modality. (143, 150) It decreases the perioperative morbidity while its efficacy is comparable to that of laparotomy in women with early stage disease. (143, 151, 152)

The Gynaecologic Oncology Group (GOG) published the results of the largest randomised control trial comparing laparoscopy to laparotomy in patients with newly diagnosed endometrial carcinoma.(150, 153) The study revealed the following(150):

- The conversion rate from laparoscopy to laparotomy was 25%
- The ability to retrieve pelvic lymph nodes and median pelvic nodes was similar
- Para-aortic nodes were successfully retrieved in 94% of cases randomised to laparoscopy compared to 97% of those randomised to laparotomy
- The detection of nodal disease was the same in both groups
- The rate of postoperative complications, median blood loss and median length of hospital stay were significantly lower in patients randomised to laparoscopy

A meta-analysis of four randomised control trials comparing laparoscopically assisted or total laparoscopic hysterectomy in women undergoing complete surgical staging for endometrial caracinoma found laparoscopic procedures to have the following benefits: It had fewer perioperative complications, decreased blood loss (267ml less), a shorter hospital stay (3 vs. 4 days) and a faster return to normal activity (28 vs. 48 days). Operative time is, however, much longer (3.3 vs. 2.2 hours). (143, 154)

Intraoperative lymph node assessment

Endometrial carcinoma is a surgically staged malignancy. The results of two randomised trials comparing pelvic lymphadenectomy to no lymphadenectomy, demonstrated that lymphadenectomy improved surgical staging but did not result in improved survival (Panici et al., 2008; ASTEC Study Group, 2009). There is general consensus that the value of lymphadenectomy in truly low risk cases is questionable. The problem still lies in identifying these low risk cases using preoperative and intraoperative features.

Currently the only way to most accurately identify the presence of microscopic nodal disease is with a comprehensive pelvic and para-aortic lympadenectomy. Lymphadenectomy is not therapeutic by itself, and the results of the lymphadenectomy must be used to guide decisions regarding adjuvant therapies (Leitao and Barakat, 2011).

Extra uterine disease, and especially para-aortic and pelvic lymph node metastases, is an important prognostic factor for endometrial carcinoma. The approach to lymph node assessment is still a controversial topic, especially in patients presumed to have early stage disease. (143) The rate of nodal spread is dependent on both tumour grading and stage. It varies from 3 – 5% in patients with well-differentiated, superficially invasive tumours, to 20% in patients with poorly differentiated, deeply invasive cancers. (143, 155–157)

The following factors indicate a high risk of lymph node involvement, and even patients presumed to have stage I disease may benefit from surgical resection of the lymph nodes:

- Serous, clear cell or high grade histology
- Myometrial invasion that is greater than 50%
- Large tumours (> 2cm in diameter or filling the endometrial cavity) (143)

The risk of lymph node involvement in patients with clinical stage I endometrial cancer, is summarised in the table below.

Table 4: Risk of lymph node involvement in patients with clinical stage I disease(33, 158)

Prognostic group	Patient characteristics	Risk of nodal involvement
A	Grade I tumours involving only endometrium	< 5%
	No evidence of intraperitoneal spread	
B	Grade II – III tumours	5 – 9% pelvic nodes
	Invasion of < 50% of myometrium	
	No intraperitoneal spread	4% para-aortic nodes
C	Deep muscle invasion	20 – 60% pelvic nodes
	High grade tumours	10 – 30% para-aortic nodes
	Intraperitoneal spread	

Patients with grade 1 or 2 disease that is presumed to be stage IA or IB have a greater than 90% 5 year survival rate following TAH and BSO alone. Some authors advocate only palpating the relevant nodes and sampling enlarged nodes. (121, 143, 155, 159–162) However, inspection is not a sensitive method of detecting lymph node involvement as only 10% of patients with nodal involvement will have grossly enlarged nodes. (156) It should be noted that women who do not undergo at least lymph node sampling is incompletely staged. (143)

While lymph node sampling aims to obtain a representative biopsy, the goal of lymphadenectomy is to remove all lymph nodes in a specific anatomical distribution. (143) Multiple site lymph node sampling is associated with better survival rates than limited sampling, or no sampling at all. (143, 163)

There may be para-aortic lymph node metastases, even in the absence of positive pelvic lymph nodes. (143, 164) There is some evidence to suggest that para-aortic lymph node dissection may confer a survival benefit in patients diagnosed with intermediate or high risk endometrial cancer. (143, 165)

Given the importance of lymph node assessment in staging the tumour and planning treatment, complete pelvic lymph node dissection and extended lymph node dissection is a reasonable approach. (143)

The role and method of sentinel node biopsy in detecting lymph node metastases is still unclear. (143, 166) A meta-analysis found that sentinel node biopsy has a 93% sensitivity in detecting nodal involvement in patients with endometrial carcinoma. (167)The site of injection is controversial; cervical, subserosal and hysteroscopically guided endometrial injection is possible. (143, 154, 166, 168–171)

1.10.2 Adjuvant therapy

Radiation therapy (RT) is the most common adjuvant modality for endometrial cancer. Traditionally chemotherapy was deemed ineffective. There has been a recent paradigm shift as four randomised control studies found that adjuvant whole pelvis external beam RT did

not improve disease specific or overall survival in stage I or stage II disease, despite improving local control. (172)

The following patients should receive adjuvant treatment(173):

- **Low risk disease:** Grade 1 or 2 endometrioid tumour that are confined to the endometrium requires no adjuvant treatment
- **Intermediate risk disease:** Tumours that invade the myometrium (IA or IB) or occult cervical stromal invasion are candidates for adjuvant RT. Chemotherapy may be used for patients with high intermediate risk.
- **High risk:** Patients with stage stage III disease (irrespective of histology), clear cell carcinoma and uterine serous carcinoma of any stage should receive chemotherapy with or without RT

1.11 Management options in endometrial cancer recurrence

1.11.1 Local recurrence

1.11.1.1 Surgery

Retrospective reports demonstrate that surgical resection may enhance long-term recurrence free survival in selected patients who exhibit recurrence locally after primary surgery – as long as evidence of retroperitoneal involvement or extension of the disease to the pelvic side wall is not present. Outcomes are most favourable in patients who present with an isolated vaginal recurrence and who are able to undergo complete resection. (174, 175) Surgical resection is best reserved for the woman who has recurrent disease that can be completely resected and who is a good surgical candidate.

1.11.1.2 Pelvic exenteration

Isolated central pelvic recurrence after surgery and / or radiotherapy is rare, but does occur. Pelvic exenteration is associated with a high operative morbidity, but this procedure remains the only potentially curative option for those patients presenting with central recurrence after surgery and radiotherapy. (176)

The best candidates are women who are medically fit for radical surgery and whose central vaginal recurrence is the only known site of the disease.

1.11.1.3 Radiation therapy

While attempted resection may represent an appropriate option for selected women with a localised vaginal recurrence, women with endometrial cancer are often overweight and present with co morbidities such as hypertension and diabetes mellitus. These patients represent a particularly high-risk group for radical surgery. Due to this, radiation therapy is commonly offered to women with an isolated vaginal or pelvic recurrence. In this case surgery is reserved for radiation therapy failure. Long-term survival rates in women who undergo radiation therapy after relapse range from 25 - 75%, with most reporting five-year survival rates of approximately 50% (Huh et al., 2007; Lin et al., 2005).

1.11.2 Metastatic primary disease, pelvic side wall and distant recurrence

1.11.2.1 Surgical cytoreduction

If complete resection to no gross residual disease is possible, surgical cytoreduction may confer a survival benefit in women presenting with metastases or recurrent disease involving the pelvic side wall or distant sites. (9, 177)

1.11.2.2 Hormone therapy

In patients with advanced endometrial carcinoma hormone therapy is a good treatment option, but it has certain limitations. Low grade tumours and those that express progesterone receptors (PR) are more likely to respond to hormone therapy than high grade tumours and those without hormone receptor expression. (2, 178, 179) Hormone therapy is recommended as initial therapy in patients with PR positive tumours. Chemotherapy is recommended for PR negative tumours. (180)

When several progestins are combined (e.g. medroxyprogesterone acetate, megesteril acetate, etc.) response rates of as high as 56% have been reported, with low grade tumours having the best response to therapy. (178, 181) However, some studies demonstrated response rates as low as 15 – 20%. (182)

Tamoxifen is a selective oestrogen receptor modulator (SERM). It is effective in women with advanced endometrial carcinoma with hormone receptor positive tumours. The response rate in these patients is 30 – 35%. (183)

Tamoxifen and progestin is sometimes combined, the rationale being that progestins downregulate oestrogen receptor (ER) expression, limiting the effect of tamoxifen. Tamoxifen is associated with an increased risk of endometrial cancer when used in the chemoprevention and adjuvant treatment of breast cancer due to its oestrogen agonist effects. It also increases expression of cytosolic progesterone receptors. (184)

A high percentage of endometrial carcinomas have GnRH receptors, but data on the efficacy of GnRH remains variable and inconclusive. (185, 186)

1.11.2.3 First line chemotherapy

Single agent therapy

First line monotherapy agents include doxorubicin, cisplatin, carboplantin, docetaxel, paclitaxel, topotecan and ixabepilone. Response rates vary from 12 – 28%. (187, 188)

Combination chemotherapy

Combination regimens have slightly better response rates (36 – 67%). (189)

1.11.3 Treatment of advanced or recurrent endometrial cancer

Women with metastatic or recurrent endometrial cancer represent a heterogeneous group. Depending on the previous treatment and the site of the recurrence, these patients may be managed with palliative or curative intent. Treatment options for recurrent disease include radiation therapy, surgery, hormone therapy and cytotoxic chemotherapy.

Cure is not likely unless the localised recurrence is limited to the vaginal cuff. This demonstrates the importance of close surveillance and monitoring after primary treatment with routine vaginal cytology and pelvic examinations.

Endometrial cancer recurs in approximately 3 - 17% of women initially diagnosed with early stage endometrial cancer. (103, 190) Local recurrences predominate in women treated with surgery alone, while distant recurrences are more common in women treated with combined modalities. (191)

Factors that predispose to the recurrence of endometrial cancer include: higher staged carcinomas, myometrial or cervical invasion, lymphatic spread, and histological subtype. (103) Papillary serous, clear cell and endometrioid carcinomas have the highest risk of recurrence. (103, 192) High-grade histological subtypes are also associated with have a higher risk of recurrence. (127)

The vagina is the commonest site for recurrence, but it also has the best prognosis. (103, 179)

1.12 Special clinical situations

1.12.1 Synchronous ovarian and endometrial tumours

Synchronous primary endometrial and ovarian tumours occur in 5% of patients with endometrial cancer and 10% of women with ovarian cancer. (143, 204, 205) Premenopausal women have a 5 – 29% higher risk of synchronous primary tumours. (143, 206)

Synchronous primary tumours do not change the staging or operative treatment of endometrial cancer. (143)

1.12.2 Inoperable patients

Radiation therapy is an acceptable alternative in stage I patients who are medically unfit or unwilling to have surgery. These patients are staged according to the 1971 FIGO classification, and staging procedures include examination under anaesthesia, sounding of the uterus, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy and imaging studies. (143)

A retrospective review found that women older than 75 years who had either external beam radiation therapy and / or brachytherapy as they were poor surgical candidates, had disease specific survival rates of 93% and 73% at 1 and 3 years, respectively. Both groups had an overall survival rate of 28% at 2 years. (207)

1.12.3 Fertility preservation

Women of childbearing age with grade 1 or grade 2 endometrioid endometrial malignancy that is confined to the endometrium may be candidates for fertility preservation. Progestin

therapy is the mainstay of treatment in this group.(91, 208) Patients should be counselled extensively to allow them to make an informed decision. (208)

A thorough evaluation prior to therapy (including dilation and curettage and imaging studies) should be done to confirm that the lesion is in fact consistent with the above criteria. (143, 208)

1.13 Post treatment surveillance

Post treatment surveillance consists mainly of monitoring the patient for symptoms and physical examination.

The use of CA – 125 in posttreatment surveillance is controversial. (209) It may have a role in follow up if the initial levels were elevated. (143) Routine use of CA – 125 varies greatly across institutions. (209)It is recommended that CA – 125 only be monitored when clinically indicated. (209, 210)

Vaginal cytology after initial treatment for endometrial cancer has a sensitivity of 40% in detecting vaginal recurrence and has poor detection rates compared to physical examination alone. (209, 211)

The United States National Comprehensive Cancer Network and Society for Gynecologic Oncology made the following recommendations (209):

- Symptom review and clinical exam (including bimanual pelvic and speculum examination) every 3 – 6 months for two years, then every 6 – 12 months thereafter
- Genetic counselling for patients with a family history of Lynch syndrome

1.14 Survival rates

Appropriately treated endometrial adenocarcinoma have a survival rate of 80%. (190) More than 70% of women have FIGO stage I endometrial cancer, which carries a good prognosis. Stage III and IV disease carry a worse prognosis, but occurs only in 13% of cases. The mean survival time for stage III and IV endometrial carcinoma is 9 – 10 months. (212) Older age is associated with a poorer prognosis. (2)

Table 5 shows the FIGO surgical stage and overall survival for endometrial cancer. This data is for patients treated between 1999 and 2001. The initial (1988) FIGO classification system is used. (23)

Table 5: Endometrial carcinoma - FIGO surgical staging and overall survival rate (1988)

FIGO stage	Overall survival (%)	
	2 years	5 years
Stage I		
IA	97	91
IB	97	91
IC	94	85
Stage II		
IIA	93	83
IIB	85	74
Stage III		
IIIA	80	66
IIIB	62	50
IIIC	75	57
Stage IV		
IVA	47	26
IVB	37	20

1.15 Rationale

Currently the management of endometrial carcinoma is individualised to the patient's profile, fertility options and availability of surgical resources and expertise. Currently there is no uniform screening protocol for endometrial cancer. This study aims to determine the predisposing factors, symptoms, treatment options and outcome in women with endometrial carcinoma in the South African context. This would enable us to make recommendations

regarding monitoring and implementing medical and surgical interventions with the least risk of morbidity and mortality.

1.16 Aim

To determine the clinical profile and management of women treated for endometrial carcinoma in Durban, South Africa.

1.17 Objectives of the study

- To determine the clinical profile and risk factors of women presenting with endometrial carcinoma
- To determine the frequency of the various stages of endometrial carcinoma
- To determine the different management modalities
- To determine the different subtypes of endometrial carcinoma
- To determine the frequency and type of complications following treatment in women with endometrial carcinoma
- To determine the number of women presenting with recurrent disease during the study period
- To determine if HIV status influences the outcome of treatment in women with endometrial carcinoma

CHAPTER 2:

METHODOLOGY

2.1. Study design and location of study

This study was a retrospective chart review of all patients presenting to the Combined Gynaecology Oncology Clinic at Inkosi Albert Luthuli Central Hospital (IALCH) from the 1January 2005 to 31 December 2010, with a histological diagnosis of endometrial carcinoma.

2.2. Materials and methods

The inclusion criteria were as follows:

- All women presenting to the Combined Gynaecology / Oncology Clinic at IALCH between 1 January 2005 and 31 December 2010 with a histological diagnosis of endometrial carcinoma

The exclusion criteria were:

- Women with other types of carcinomas

Eligible women were identified from a clinical database at IALCH, as all clinical information is captured on the Medicom database. As IALCH functions as a tertiary referral centre all patients referred to IALCH with endometrial carcinoma are reviewed at the combined oncology clinic. Two hundred case files with a diagnosis of endometrial carcinoma were reviewed and all relevant variables were recorded onto a structured data sheet (Annexure 1).

The study variables studied included:

- Race
- Age
- Age at menarche
- Age at menopause
- Obesity (BMI)
- Parity
- Polycystic ovarian syndrome (PCOS)
- Hypertension
- Diabetes mellitus
- Familial predisposition
- History of breast cancer
- History of combined oral contraceptive use
- Postmenopausal bleeding
- FIGO staging of the endometrial carcinoma
- Histological subtype of endometrial carcinoma
- Radiation therapy to the pelvis
- HIV status
- Management and postoperative complications

Pathological staging in this study was designated according to the 1988 FIGO Classification of Endometrial Cancer. In 2009 FIGO introduced revised staging criteria for endometrial cancer. In the unit where the data was collected from 2005 – 2010, the 1988 FIGO classification was used.

Confidentiality of all subjects was maintained by allocating a study number and no names were recorded on the data sheet (Annexure 1).

Pap smear results were grouped into normal or abnormal. Abnormal Pap smear included those women who had low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL) or Human papilloma virus (HPV).

On the basis of body mass index (BMI) (calculated as weight [kg]/height [m]^2), patients were classified into five groups: Underweight (BMI < 20), normal weight (BMI: 20 - 24.9), overweight (BMI 25 - 29.9), obese (BMI 30 - 35) and morbidly obese (BMI ≥ 35).

Length of hospital stay was defined as duration of hospitalisation from admission to discharge.

2.3. Statistical analysis

Data was electronically captured using MS Excel and imported into SPSS version 22 (SPSS Inc, Chicago) for analysis. Descriptive analysis was performed. Categorical variables were presented as frequency counts and percentages while quantitative variables were summarised using mean, standard deviation and range. A p - value < 0.05 was considered to be statistically significant. A p - value was obtained using the analysis of variance (ANOVA) test for the study variables (age, surgery time, hospital stay) in the different BMI groups.

2.4. Ethical considerations

The study was approved by the Biomedical Research Ethics Committee (BREC), Postgraduate Committees of the University of KwaZulu Natal, the hospital management of IALCH and KZN Department of Health. Ethics number REF: BE: 313/12 (Annexure 4).

CHAPTER 3:

RESULTS

3.1. Introduction

During the 6 year study period extending from 1 January 2005 to 31 December 2010,16 279 malignancies were identified at first visit to Inkosi Albert Luthuli Central Hospital (IALCH). Of the 16 279 malignancies from the oncology database, there were 3 002 gynaecological malignancies, giving a proportion of 18.4% (3 002 / 16 279).

After analysis of patient records, 200 (6.7%) of the 3 002 gynaecological malignancies were diagnosed with endometrial carcinoma. The yearly distribution of endometrial carcinomas is shown in Table 6.

Table 6: Yearly distribution of endometrial carcinoma at IALCH

Year	No. of endometrial carcinomas / No. of gynaecological cases (%)
2005	31 / 200 (15.5)
2006	29 / 200 (14.5)
2007	31 / 200 (15.5)
2008	38 / 200 (19.0)
2009	35 / 200 (17.5)
2010	36 / 200 (18.0)

3.2. Demographics and clinical characteristics

The mean ± SD age of the 200 patients was 63.8 ± 9.4 (range: 23 – 83) years. The median age was 64.5 years. Thirteen (6.5%) patients were below the age of 50 years and 187

(93.5%) of the patients were above 50 years of age. The median parity was 4. The majority (n = 123; 61.5%) of patients were in the 1 - 4 parity group.

The study population consisted of four racial groups. Ninety five (47.5%) were Indian, 92 (46%) were Black, 12 (6%) were White, and 1 (0.5%) was Coloured. There was no difference in the age (years) between Indian and Black patients, who made the greater part of our study population (63.2 ± 9.7 vs. 64.5 ± 9.3; p = 0.3), but there was a significant difference in the BMI between the two racial groups (29.6 ± 3.9 vs. 32.2 ± 7.6; p < 0.004).

Table 7: Comparison of demographic details in black and Indian populations

Variable	Black (n = 92; 46%)	Indian (n = 95; 47.5%)	White (n = 12; 6%)	Coloured (n = 1; 0.5%)	p-value
Age	64.5 ± 9.3	63.2 ± 9.7	63.4 ± 6.2	62	0.03
BMI	32.2 ± 7.6	29.6 ± 3.9	29.8 ± 4.2	32	0.04

HIV status was documented as positive in 13 (6.5%) cases and negative in 187 (93.5%) cases. All 200 patients had validated HIV test results.

Thirteen (6.5%) patients presented with abnormal uterine bleeding in the premenopausal period. One hundred and eighty seven (93.5%) patients presented with postmenopausal bleeding. Demographic details of the study population are shown in Table 8.

Table 8: Demographic details of women with endometrial carcinoma

(n = 200)

Age (years) Mean ± SD (range)	63.8 ± 9.4 (23 – 83)
Parity Median (range)	4 (0 – 11)
Parity groups (%) Nulliparous Low parity (1 – 2) Multiparous (3 – 4) Grand multiparous (≥ 5)	 32 (16) 34 (17) 89 (44.5) 45 (23.5)
Racial groupings (%) Indian White Black Coloured	 95 (47.5) 92 (46) 12 (6.0) 1 (0.5)
HIV status (%) Negative Positive	 187 (93.5) 13 (6.5)
Presenting symptoms at diagnosis (%) Abnormal uterine bleeding Postmenopausal bleeding	 13 (6.5) 187 (93.5)
Haemoglobin in g/dl Mean ± SD (range) Median	 10.88 ± 1.2 (6.8 – 14) 10.6
Transvaginal ultrasound (%) Yes No	 10 (5.0) 190 (95.0)

3.3. Histopathological results at diagnosis

Table 9 lists the histopathological results.

Table 9: Histopathological results (n = 200)

Histological type	Number (n=200)	Percentage (%)
Endometrioid	147	73.5
Carcinosarcoma	32	16.0
Serous	17	8.5
Clear cell	4	2.0

3.4. Histopathological results in different race groups

Ninety two (46%) black patients and 95 (47.5%) Indian patients were diagnosed with endometrial carcinoma. There was a significant difference between the groups with respect to the endometrioid type (86.3% vs. 58.7%; $p < 0.001$) and carcinosarcoma, serous and clear cell subtypes (13 vs. 38; $p < 0.001$). Histopathological results in the different racial groups are listed in Table 10.

Table 10: Comparison of histopathological results in the black and Indian population

Histopathological findings	Black n (%)	Indian n (%)	White n (%)	Coloured n (%)	p-value
Endometrioid	54 (58.7)	82 (86.3)	11 (91.7)	0	0.0001
Carcinosarcoma	23 (25)	7 (7.4)	1 (8.3)	1 (100)	0.001
Serous	12 (13)	5 (5.3)	0	0	0.07
Clear cell	3 (3.3)	1 (1.0)	0	0	0.2

3.5. Predisposing factors affecting endometrial carcinoma

3.5.1. Endometrial carcinomas by age

One hundred and eighty seven (93.5%) endometrial carcinomas occurred in patients over 50 years of age. Thirteen (6.5%) endometrial carcinomas occurred in patients under 50 years of age. Endometrial carcinomas stratified into different age groups are shown in Table 11.

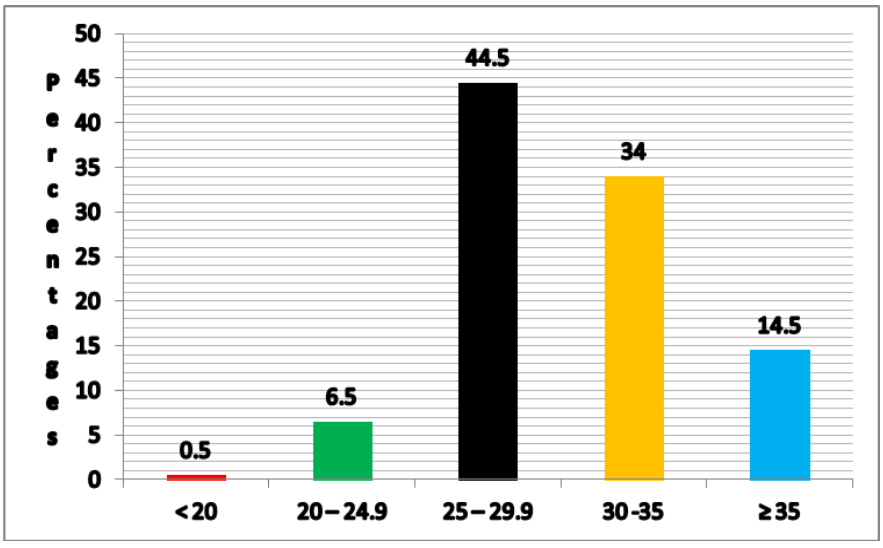
Table 11: Number of endometrial carcinomas by age

Age (years)	**Number**	**%**
20 – 29	1	0.5
30 – 39	3	1.5
40 – 49	9	4.5
50 – 59	41	20.5
60 – 69	91	45.5
70 – 79	51	25.5
≥ 80	4	2.0

3.5.2. Endometrial carcinomas by body mass index

Endometrial carcinomas by body mass index are graphically depicted in Figure 1. There was 1 (0.5%) patient who was classified as underweight with a BMI < 20, 13 (6.5%) patients were classified as normal weight (BMI 20 – 24.9), 89 (44.5%) patients were classified as overweight (BMI 25 – 29.9), 68 (34%) patients were classified as obese (BMI 30 – 35) and 29 (14.5%) patients were classified as morbidly obese with a BMI ≥ 35.

Figure 1: Graphical representation of body mass index



3.5.3. Other predisposing factors for endometrial carcinoma

Other predisposing factors affecting endometrial carcinoma are shown in Table 12.

Table 12: Predisposing factors affecting endometrial carcinoma

Factor	Data
Menarche (years)	
Mean ± SD	14.4 ± 1.2 (range: 9 19)
Median	14
Categorisation of menarche (years)(%) (n=128)	
≤ 12	4 (3.1)
13 – 14	113 (88.3)
≥ 15	11 (8.6)
Menopause (%)	
Yes	187 (93.5)
Mean ± SD at menopause (years)	51.05 ± 2.6 (range: 37 – 60)
Median	51
No	13 (6.5)
Polycystic ovarian syndrome (%)	
Yes	5 (2.5)
No	195 (98.5)
Ca of breast (%)	
Yes	14 (7)
No	186 (93)
Tamoxifen (%)	
Patients receiving tamoxifen	4 (2)
Comorbidities (%)	
Hypertension	108 (54)
Diabetes	8 (4)
Hypertension and diabetes	52 (26)

Endometrial thickness (mm)	
Mean ± SD	22.1 ± 5.9 (range: 5 – 44)
Median	22
Hormone replacement therapy (%)	
Yes	113 (56.5)
Type of HRT	
- Oestrogen	75 (66.4)
- Oestrogen and progesterone	38 (33.6)
No	87 (43.5)
Combined oral contraceptive (years) (%)	
Yes	55 (27.5)
Duration of COC use (mean ± SD)	6.15 ± 1.2 (range: 3 – 10)
No	145 (72.5)
Parity (%)	
Nulliparous	32 (16)

3.6. Methods of diagnosing endometrial carcinoma

Table 13: Methods of diagnosing endometrial carcinoma

Postoperative modality	Number	Percentage
Dilatation and curettage	7	3.5
Pipelle	193	96.5

3.7. Cervical Papanicolaou Smear results

Abnormal Pap smear results were observed in 88 (44%) patients. Pap smear results are shown in Table 14.

Table 14: Cervical Papanicolaou smear results

Pap results	Number	Percentage
Normal	112	56
LGSIL	52	26
HGSIL	9	4.5
HPV	27	13.5

Table 15: Relationship between abnormal cervical cytology and type of endometrial carcinoma

Type of endometrial cancer (n = 200)	**Abnormal cervical cytology**	**Percentage**
Endometrioid (n = 147)	62	42.2
Carcinosarcoma (n = 32)	17	53.1
Serous (n = 17)	8	47.1
Clear cell (n = 4)	1	25

3.8. Treatment of endometrial adenocarcinoma

Twenty nine (14.5%) patients were managed medically and 171 (85.5%) were managed surgically.

3.8.1. Non-surgical therapy

Twenty nine patients received radiotherapy and chemotherapy. (Table 16)

Table 16: Primary mode of non-surgical therapy (n=29)

Primary mode of non-surgical treatment	**Yes** (n)(%)	**No** (n)(%)	**p-value**
External-beam radiotherapy and chemotherapy	14 (48.3)	15 (51.7)	0.7
External-beam radiotherapy	11 (37.9)	18 (62.1)	0.06
Vaginal brachytherapy	3 (10.3)	26 (89.7)	0.0001
Chemotherapy	1 (3.5)	28 (96.5)	0.0001

3.8.2. Surgical therapy

One hundred and seventy one (85.5%) patients had surgical intervention. The peri operative parameters of these women are shown in Table 17. One hundred and fifty (87.7%) of these women were treated with adjuvant radiotherapy and / or chemotherapy, according to pathological findings at time of surgery. In 21 (12.3 %) patients surgical therapy was the only mode of therapy.

Type of surgery

- Total abdominal hysterectomy and bilateral salpingo-oopherectomy (n = 161)
- Vaginal hysterectomy (n = 5)
- Laparascopic assisted vaginal hysterectomy (n = 5)

Duration of surgery

The mean ± SD (range) duration of surgery was 83.9 ± 12.9 (60 – 120) minutes. The median duration of surgery was 80 minutes.

Hospital stays

The mean ± SD (range) number of days of hospital stay was 7.7 ± 0.9 (4 - 11) days. The median number of days confinement at hospital was 8 days.

Adjuvant therapy following surgery

The adjuvant therapy received by patients is as follows (n = 150):

- External-beam radiotherapy + chemotherapy (n = 57)
- Vaginal brachytherapy + chemotherapy (n = 6)
- External-beam radiotherapy (n = 56)
- Vaginal brachytherapy (n = 31)

Table 17: Peri operative parameters of women having primary surgical treatment (n=171)

	Number (%)
Procedure TAH + BSO Vaginal hysterectomy Laparoscopically assisted vaginal hysterectomy / BSO	 161 (94.2) 5 (2.9) 5 (2.9)
Duration of surgery (min) Mean ± SD Range Median	 83 ± 12.9 60 – 120 80
Hospital stay (days) Mean ± SD Range Median	 7.7 ± 0.9 4 – 11 8
Postoperative complications (%) Wound sepsis Deep vein thrombosis Urinary tract infections Wound haematoma	 5 (25) 4 (20) 3 (15) 8 (40)

3.9. Perioperative variables based on body mass index

Table 18: Perioperative variables based on body mass index

BMI	Normal	Overweight	Obese	Morbidly obese	p - value
Number of patients	13	89	68	29	
BMI*	23.2 ± 1.6	27.9 ± 1.4	34.8 ± 6.0	41.6 ± 7.6	0.0001
Age (years)*	60.3± 13.3	63.4 ± 9.0	64.7 ± 9.0	63.45 ± 8.4	0.1
Surgery time (min)*	82.5 ± 12.7	81.3 ± 11.5	86.6 ± 13.5	92.3 ± 16.7	0.07
Hospital stay (days)*	7.9 ± 1.1	7.7 ± 1.0	7.7 ± 0.9	8.1 ± 1.1	0.6

* Expressed as mean ± SD

3.10. Complications following surgical procedures

Twenty (11.7%) of the 171 patients who had undergone surgery developed complications. Eight (4.7%) patients developed wound haematomas, 5 (2.9%) had wound sepsis, 4 (2.3%) developed deep vein thrombosis and 3 (1.8%) had urinary tract infection. Complications are listed in Table 19.

Eighteen (11.2%) complications occurred in patients who had total abdominal hysterectomy and bilateral salpingo-oophorectomy, 1 (20%) in a patient who had a vaginal hysterectomy and 1 (20%) in a patient who had a laparoscopically assisted vaginal hysterectomy.

Table 19: Complications following different surgical procedures

Surgical procedure	TAH + BSO n=161 (%)	VH n=5 (%)	LAVH n=5 (%)
Wound sepsis	5 (3.1)	0 (0)	0 (0)
Deep vein thrombosis	3 (1.9)	0 (0)	1 (20)
Urinary tract infections	3 (1.9)	0 (0)	0 (0)
Wound Haematoma	7 (4.3)	1 (20)	0 (0)
Total	**18 (90)**	**1 (5)**	**1 (5)**

Perioperative complications were not associated with age (p = 0.36), race (p = 0.39) and cancer stage (p = 0.45). Perioperative complications were associated with a prolonged hospital stay (p = 0.02).

3.11. Relationship between complications and BMI

The number of perioperative complications occurring with an increased BMI, are shown in Table 20. There was a significant association between BMI (obese 31% vs. normal 3%) and perioperative complications (p < 0.001).

Table 20: Number of complications based on BMI (n=109)

Variable	BMI	Number of complications	%
Normal (n = 13)	20 – 24.9	3	23.1
Overweight (n = 89)	25 – 29.9	48	53.9
Obese (n = 68)	30 -35	34	50
Morbidly obese (n = 29)	≥ 35	23	79.3

3.12. Post-surgical management of women with endometrial carcinoma

Table 21: Post-surgical management of women with endometrial carcinoma (n = 200)

Postoperative modality	Number (%)
Low molecular weight heparin	
Yes	63 (31.5)
No	137 (68.5)
Physiotherapy	
Yes	31 (15.5)
No	169 (84.5)
Radiotherapy	
Yes	176 (88)
No	23 (11.5)
Unknown	1 (0.5)
Types of radiotherapy	
External beam	135 (76.7)
Brachytherapy	41 (23.3)
Chemotherapy	
Yes	77 (38.5)
No	117 (58.5)
Unknown	6 (3.0)

3.13. Staging of endometrial adenocarcinoma

As only 5 of the 200 patients underwent pelvic or para-aortic lymphadenectomy, the staging of endometrial carcinoma is incomplete.

Table 22A: Incompletely staged endometrial carcinoma

STAGING OF ENDOMETRIAL CARCINOMA	FREQUENCY
Ia	18
Ib	66
Ic	32
TOTAL	**116**
IIa	25
iib	11
TOTAL	**36**
IIIa	26
IIIb	6
IIIc	5
TOTAL	**37**
IVa	9
IVb	2
TOTAL	**11**

The frequency of the various stages of endometrial carcinoma is depicted in Table 22B.

Table 22B: Distribution of histological subtypes by stage

	Histology result				
Staging	**Endometrioid** n = 147 (73.5%)	**Carcinocar-cinoma** n = 32 (16%)	**Serous** n = 17(13.5%)	**Clear cell** n = 4 (2%)	**Total** n = 200 (100%)
Ia	16 (10.9)	2 (6.3)	0 (0)	0 (0)	18 (9)
Ib	53 (36.1)	12 (37.5)	1 (5.9)	0 (0)	66 (33)
Ic	24 (16.3)	5 (15.6)	2 (11.8)	1 (25)	32 (16)
IIa	15 (10.2)	5 (15.6)	3 (17.6)	2 (50)	25 (12.5)
IIb	9 (6.1)	1 (3.1)	1 (5.9)	0 (0)	11 (5.5)
IIIa	17 (11.6)	4 (12.5)	5 (29.4)	0 (0)	26 (13)
IIIb	3 (2.0)	0 (0)	3 (17.6)	0 (0)	6 (3)
IIIc	4 (2.7)	0 (0)	0 (0)	1 (25)	5 (2.5)
IVa	4 (2.7)	3 (9.4)	2 (11.8)	0 (0)	9 (4.5)
IVb	2 (1.4)	0 (0)	0 (0)	0 (0)	2 (1)

3.14. Recurrence details

3.14.1. Demographic profile of endometrial carcinoma recurrence

Table 23: Demographic profile of endometrial recurrence

	Number (%)
Total recurrences	28 (14)
Age (years) at recurrence Mean ± SD Range Median	 63.96 ± 8.5 47 – 81 64
Site of recurrence Vaginal vault Pelvis Distant	 12 (42.86) 9 (32.14) 7 (25.0)
Time elapsed following initial treatment (months) Mean ± SD Range Median	 21 ± 25.2 2 – 120 12

3.14.2 Histology type and recurrence of endometrial carcinoma following treatment

The number of recurrences according to histology type is shown in Table 24.

Table 24: Histological type at diagnosis and recurrence of endometrial carcinomas following treatment

Histology type	Recurrence (n = 28)	Percentage
Endometrioid (n = 147)	22	15.0
Carcinosarcoma(n = 32)	5	15.6
Serous (n = 17)	1	5.9
Clear cell (n = 4)	0	0.0

3.14.3. Initial treatment of endometrial carcinomas that recurred

Table 25: Initial treatment of endometrial carcinomas that recurred

Treatment	Recurrence (%)
Adjuvant therapy following surgery (n=150)	27 (18)
External beam radiotherapy & chemotherapy	15 (10)
Vaginal brachytherapy & chemotherapy	2 (1.3)
External beam radiotherapy	7 (4.7)
Vaginal brachytherapy	3 (2)
Non-surgical (medical) (n=29)	1
External beam radiotherapy & chemotherapy	1

3.14.4. Cytology, histology and staging results of patients with endometrial carcinoma recurrence

Results of patients with recurrence of endometrial carcinoma is shown in Table 26.

Papanicolauo result of patients with recurrence of endometrial carcinoma

Sixteen (57.14%) of the 28 patients who had recurrence presented with abnormal Pap smears.

Pipelle result

The Pipelle results, of the 28 patients who had recurrence, showed that 25 (89.3%) patients were diagnosed with endometrial carcinoma and 3 (10.7%) were non-representative.

Table 26: Cytology, histology and staging results of patients with endometrial carcinoma recurrence

Pap result	Number	Percentage
Normal	12	42.9
Abnormal	16	57.1
Low grade squamous intraepithelial lesion	8	50.0
High grade squamous intraepithelial lesion	3	18.8
Human papilloma virus	5	31.2
Pipelle result		
Non-representative	3	10.7
Carcinoma	25	89.3
Staging		
IA	2	7.14
IB	11	39.30
IC	7	25.00
IIA	2	7.14
IIB	0	0
IIIA	2	7.14
IIIB	2	7.14
IIIC	0	0
IVA	2	7.14
IVB	0	0

CHAPTER 4:

DISCUSSION

4.1. Discussion

In our study, the proportion of endometrial carcinoma to the total number of gynaecological malignancies was 6.7% over the 6-year study period.

The age of diagnosis of endometrial carcinoma peaks in the seventh decade of life. In our audit, the median age at presentation of endometrial carcinoma was 64.5 years, compared to 60 years of age in the USA. (11)The worldwide median age at diagnosis is 63 years.(67) Thirteen (6.5%) patients were premenopausal and187 (93.5%) were postmenopausal. Previous studies have suggested that up to 14% of women with endometrial carcinoma are premenopausal. (213) It has been reported that women younger than 40 years of age make up 5% of endometrial carcinoma cases, and 10 – 15% of cases occur in women less than 50 years of age.(180) Thirteen (6.5%) of our patients were below the age of 50 years and 4 (2%) were below 40 years of age. This is consistent with international studies which have shown that 5 - 30% of the endometrial cancer population is found to be premenopausal.(214)

In our study the majority of the endometrial carcinomas occurred in the 60 - 69 age group, compared to the 50 - 54 age group in a study done in 1996 by McPherson et al. (78) In a more recent study, Ali reported two peaks (age 55 - 59 years, and 65 - 69 years) at which endometrial carcinoma occurred.(215)

All the patients in this study population presented with postmenopausal bleeding. This is likely due to late presentation of patients in the background of a resource limited setting. Seven (3.5%) endometrial carcinomas were diagnosed by dilatation and curettage compared to193 (96.5%) diagnosed by Pipelle endometrial biopsy.

The sensitivity of endometrial biopsy for the detection of endometrial abnormalities is reportedly as high as 96%.(17)

Increased age and obesity were important predisposing factors for endometrial carcinoma that were identified in this study. In the USA, age, obesity and unrestricted use of oestrogen therapy were listed as being important risk factors for the development of endometrial carcinoma.(67) In this study the risk of endometrial carcinoma was about seven times higher in overweight patients, and five times higher in obese women compared to patients with normal weight. In a recent study, it has been reported that endometrial carcinoma risk is 32% higher in overweight women and 2.5 times higher in obese women compared to women with a healthy weight.(216) In this study 75 (66.4%) patients were exposed to unopposed oestrogen despite the associated increased risk for endometrial carcinoma. This is an alarming statistic as these patients should ideally have received add-back progestin therapy.

Obesity was significantly associated with operating time. One of the reasons postulated is that in obese patients there is greater difficulty in operative access. There were more perioperative complications in women with increased BMI (obese 31% vs. normal 3%), which was found to be statistically significant.

Immune deficiency has been implicated in endometrial carcinoma. (127)In our study, 13 (6.5%) women with endometrial carcinoma were infected with HIV. None of the women who were HIV positive in our study had recurrence during the study period. In addition to the AIDS-defining cancers such as non-Hodgkin's lymphoma, Kaposi's sarcoma, and cervical cancer, higher rates of Hodgkin's disease and anal cancer have been consistently reported to be associated with HIV / AIDS patients. (217–219) HIV status as a risk factor for endometrial carcinoma needs to be addressed further in a larger study.

Patients who have breast carcinoma are often treated with tamoxifen to reduce the risk of recurrence. In our study, 4 (28.6%) of the 14 patients with breast cancer were treated with tamoxifen. Tamoxifen acts as an anti-oestrogen in breast tissue, but it has an oestrogenic effect in the uterus and can cause endometrial hyperplasia, which has the potential for malignant change.(220) Despite the increased risk of endometrial cancer in tamoxifen users, international guidelines do not recommend routine endometrial surveillance in asymptomatic patients. (87, 94)

Eighty eight (44%) patients with endometrial carcinoma had abnormal Pap smears, with no evidence of abnormal endometrial cells. Patients presenting with HSIL or persistent LSIL were referred for colposcopy and LLETZ biopsy. Patients with postmenopausal bleeding and abnormal cervical cytology warrant careful clinical examination and investigations to exclude cervical cancer, which is more common in the South African setting. A negative Pap smear does not rule out the presence of endometrial cancer and it should not be used as a diagnostic test for endometrial carcinoma. Bakkum-Gamez et al. suggest that menopausal or perimenopausal patients with atypical / neoplastic endometrial cells on the Pap smear should be further investigated for endometrial neoplasia. (117) Münstedt et al. reported that a positive Pap smear result might have prognostic significance.(120) In a more recent study by Jones et al. one hundred and forty nine women demonstrating cytologically benign endometrial cells on Pap smear were followed up within a 12 month period. The results showed that 60.84% had no endometrial pathology, 35.66% presented with benign pathologic changes and 3.50% demonstrated endometrial carcinoma.(221)

Advancing age was identified as an important risk factors for endometrial carcinoma. In our study 187 (93.5%) endometrial carcinoma cases occurred in women older than 50 years of age, with a median age of 64.5 years. Four (2%) patients were under the age of 40 years. Endometrial carcinoma can occur at any reproductive age. (213) Early menarche, defined as menarche occurring prior to 12 years of age, is associated with endometrial cancer.(222) The results of a pooled analysis demonstrated that endometrial carcinoma risk among parous women is 11% higher in those aged < 13 years at menarche compared with those aged > 13 years at menarche. (223) Menarche in 4 of our patients occurred at < 12 years of age. Ali reported that early menarche, which ranged between 11-14 years, occurred in 45.3% of their endometrial carcinoma patients. (215)

Fifty five (27.5%) patients had a history of combined oral contraceptive use. The mean duration of combined oral contraceptive use was 6.15 (range: 3 – 10) years. In a case controlled study, Urban et al. compared women who had never used hormonal contraceptives to women who used oral and / or injectable contraceptives for a total of 5 years or longer. The women in the latter group had a significantly lower risk of endometrial cancer, whilst women who used these contraceptives for less than 5 years had no significant difference in risk.(224)

A number of epidemiological studies reported diabetes(225, 226) and hypertension(43, 227) to be a risk factor for developing endometrial cancer. One hundred and eight (54%) patients in the audit were hypertensive, 8 (4%) were diabetic and 52 (26%) were both hypertensive and diabetic. Hypertension and diabetes mellitus are both influenced by lifestyle and associated with an increased BMI.

The measurement of endometrial thickness by TVUS is used to determine the risk of endometrial carcinoma in women presenting with postmenopausal bleeding. There are conflicting reports on the endometrial thickness measurement for the exclusion of endometrial malignancy. In our study, the median endometrial thickness was 22 (range: 5 – 44) mm. Only two patients had an endometrial thickness of ≤ 5mm. A review of the clinical profile of these two patients reveals that they were both in the eight decade of life, with one having a Pap smear result showing LSIL and the other with HPV. Saha et al. found that there was an 8% chance of missing a thickened endometrium when transvaginal ultrasound is used to measure the endometrial thickness and these authors recommended that transvaginal ultrasound measurement should be interpreted with caution, and patients with persistent postmenopausal bleeding and a thin endometrium on transvaginal ultrasound should undergo a hysteroscopic examination.(126)

In our study, only 6 (3%) patients had an endometrial thickness of ≥ 10mm. Trans vaginal ultrasound was performed in only ten patients. A number of studies showed that endometrial thickness of ≤ 5mm is associated with a low risk for endometrial carcinoma.(228, 229) Smith-Bindman et al. reported that if the thickness of the endometrium is > 5mm, the risk of endometrial carcinoma is approximately 7.3% and < 0.07% if the endometrium is ≤ 5mm in postmenopausal women. (136)

In our retrospective study of two hundred patients treated for endometrial carcinoma, type I comprised 143 (71.5%) patients while 57 (28.5%) patients had type II endometrial carcinoma. Treatment consisted of surgical, non-surgical and adjuvant treatment following surgery. The overall recurrence rate was 14%.

In this study 95 (47.5%) endometrial carcinomas were diagnosed in Indian women, and 92 (46%) in black women. This must be interpreted in a context where the black population make up 86% of the population in Kwa Zulu Natal, and the Indian population make up only 7.4%.(230)

There was a significant difference in types of endometrial cancer between the groups. Eighty two (86.3%) Indian patients diagnosed with endometrial carcinoma presented with an endometrioid subtype, whereas only 54 (58.7%) black women had the endometrioid subtype. Twenty three (25%) black patients diagnosed with endometrial carcinoma presented with carcinosarcoma, whereas only 7 (7.4%) Indian women presented with this subtype. In the United States, white women are more likely to be diagnosed with endometrial cancer than African-American, Asian, or Hispanic women. (43)

Twenty (11.7%) of the 171 patients experienced perioperative complications. All the complications reported were short term. In another retrospective study of 233 women with endometrial carcinoma, 24 (10.3%) patients experienced complications. (231)

The treatment of choice for endometrial carcinoma is surgery. It is estimated that over 90% of women with endometrial cancer receive primary surgical management. (192)In our study 29 (14.5%) patients were managed non-surgically. This included 3 patients who were medically unfit for surgery. The non-surgical treatment included vaginal brachytherapy or external beam radiotherapy and / or chemotherapy. One hundred and seventy one (85.5%) patients were treated surgically; and 150 of these patients received adjuvant radiotherapy and / or chemotherapy.

The treatment protocol at IALCH for endometrial cancer is based on surgical staging.

- Stage IA (low risk): TAH + BSO
- Stage IA (high risk), II: TAH + BSO + lymphadenectomy (pelvic and para-aortic)
- Stage III: Radiotherapy
- Stage IV: Chemotherapy or progestogen therapy

There were 2 deaths, both being diagnosed with endometrioid adenocarcinoma. Both of these patients received primary surgical treatment and adjuvant radiotherapy, and were staged as stage IIIa. One patient demised 2 years and one month after primary treatment, and the other 6 months after primary treatment.

The recurrence rate of 14% observed in our study is within the range of 3 - 17% reported in the literature.(190, 210) The sites of recurrence listed in the literature are vaginal, pelvic, and distant metastases. The commonest site of recurrence is in the vagina. (179, 232) The vaginal vault, pelvis and distant metastases were the commonest sites of recurrence in our patients, with the vagina being the most common.

The time to recurrence of endometrial carcinoma ranged from as early as 2 months to 120 months with a median of 12 months. Recurrence occurred at the vaginal vault alone in 12 (42.8%) patients. In an earlier study by Foote and Proietto, one hundred and nineteen patients treated for FIGO stage I endometrial carcinoma were reviewed retrospectively to determine if adjuvant radiotherapy reduced disease recurrence. The overall recurrence rate was 10.1%. Recurrence at the vaginal vault alone occurred in 3.4%of patients. (233)

Studies have reported time to recurrence of 24 – 36 months.(191) It has also been reported that papillary serous carcinoma, clear cell carcinoma and high-grade histological subtypes have the highest risk of recurrence. (61, 127) Twenty two (15%) of the 28 cases of recurrence in our study, occurred in patients diagnosed with type I endometrioid adenocarcinoma. Only 6 (11.3%) cases recurred in patients with type II endometrial carcinoma. Our type II carcinoma numbers were too small to make any comparison with other studies.

One hundred and sixteen (58%) of our patients were diagnosed with stage I disease. Thirty six (18%) patients had stage II disease, 37 (18.5%) had stage III disease and 11 (5.5%) patients had stage 4 disease. The National Cancer Institute reported that in the period 2006 – 2012, 67% of patients diagnosed with endometrial cancer had localised disease confined to the primary site, 21% had regional lymph node spread and 8% had distant metastases. Four percent were not staged.(234)

4.2. Limitations

The first limitation was that the study was retrospective in nature. As surgical procedures were performed by surgeons with different level of experience some study parameters, such as operative time and perioperative complications, may be influenced by the skill of the surgeon.

Comprehensive data on certain study parameters were not available. This includes, inter alia, whether or not all patients completed planned adjuvant treatment. Data obtained was limited by the amount of data recorded in patient charts.

Only 5 patients had pelvic and/or para aortic lymph node biopsies performed. Pelvic and para aortic lymphadenectomy was not performed in the unit between 2005 and 2010. This may have resulted in under staging of certain patients with endometrial carcinoma.

Transvaginal ultrasound was only performed in 10 (5%) of patients. This is an important screening modality for patients at risk of endometrial hyperplasia.

CHAPTER 5:

CONCLUSION AND RECOMMENDATIONS

5.1. Conclusion

Even though endometrial carcinoma is primarily diagnosed after menopause, it may also occur in young women of any age. This descriptive study showed that 93.5% of patients presenting with endometrial carcinoma were over 50 years of age. The most frequently diagnosed histological subtype was endometrioid adenocarcinoma (73.5%). Approximately 45.5% of patients were diagnosed in the seventh decade of life. The majority of patients presenting with endometrial carcinoma were overweight (44.5%).

Approximately 76% of patients presented with stage I or stage II disease. Surgical intervention was the treatment of choice with 171 (85.5%) patients undergoing surgical intervention, and 150 of these patients receiving adjuvant therapy. Advancing age and obesity were the two most important predisposing factors for endometrial carcinoma.

5.2. Recommendations

1. Risk factors that are modifiable include obesity, sedentary lifestyles and use of unrestricted oestrogen.
2. The complications reported are short term complications observed during hospitalisation. It would be valuable to analyse long term complications of the same study population.
3. Any patient irrespective of age with persistent vaginal bleeding should be comprehensively investigated with the aim of excluding endometrial hyperplasia or carcinoma.

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Annexure 1: Data sheet

CLINICAL PROFILE AND MANAGEMENTOF WOMEN TREATED WITH ENDOMETRIAL ADENO CARINOMA IN DURBAN, SOUTH AFRICA

STUDY No:

PARITY: RACE: 1 2 3 4

AGE AT FIRST Dx: DATE OF FIRST Dx:

AGE AT RECURRANCE: TIME TO RECURRANCE:

SITE OF RECURRANCE: 1 2

MENARCHE: MENOPAUSE: 1 2 AGE OF MENOPAUSE:

HPT: 1 2 DM: 1 2 HX Ca Breast: 1 2 PCOS: 1 2

COC USE: 1 2 DURATION OF COC USE: TAMOXIFEN USE: 1 2

HIV: 1 2 CD4 COUNT: PRESENTATION: 1 2 3

BMI: HEIGHT: WEIGHT:

PAP SMEAR RESULTS: 1 2 3 4

PIPELLE: 1 2 PIPELLE RESULTS: 1 2 3

HRT USE: 1 2 TYPE OF HRT USE: 1 2

HB: TV ULTRASOUND: 1 2 ET :

Mx: 1 2 1 2 3 SURGICAL Mx:
DURATION OF Sx:

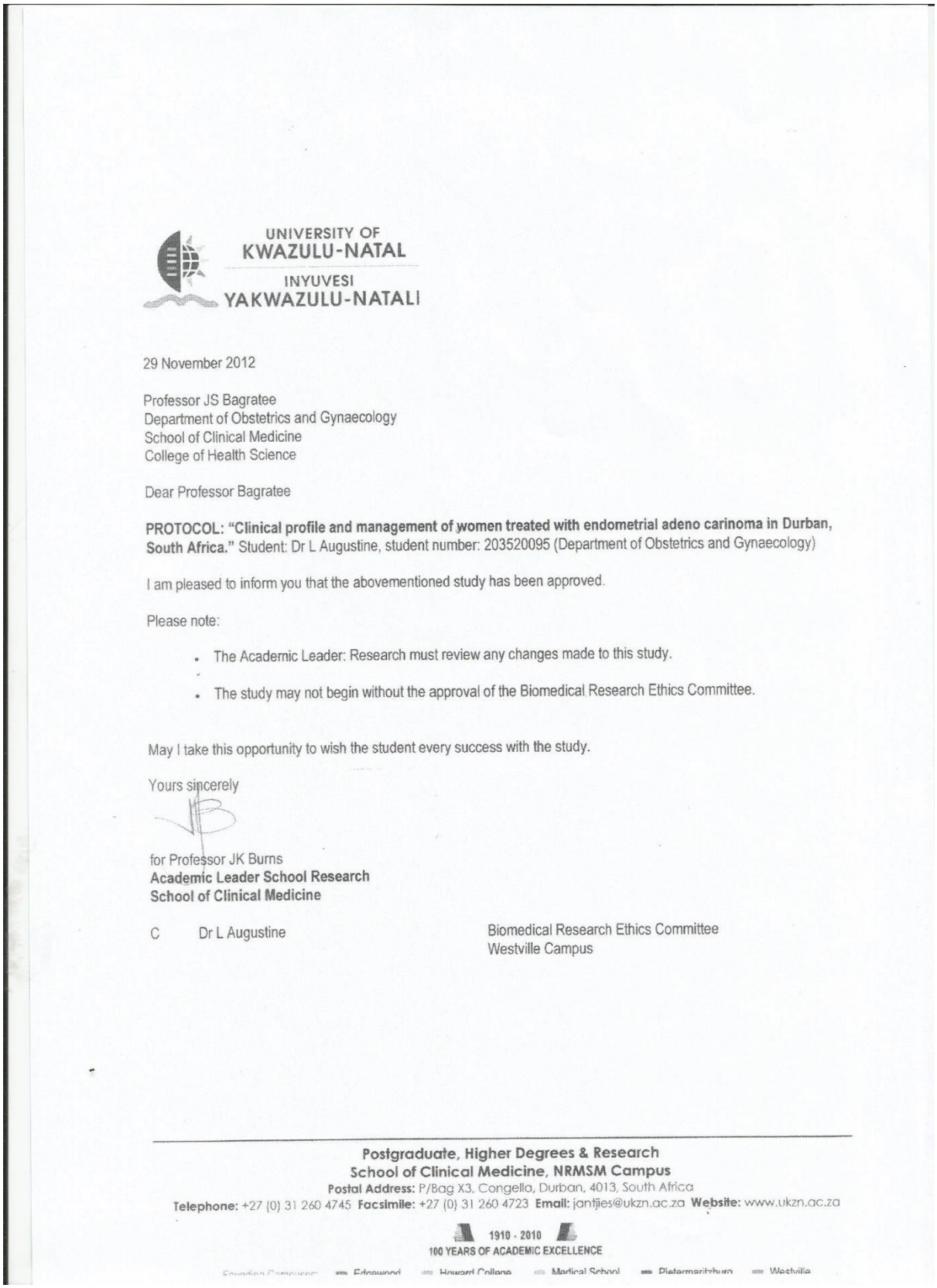
DAYS IN HOSP: POST OP COMP.: 1 2 3 4 5

USE OF LMWH: 1 2 PHYSIO: 1 2

HISTOLOGY RESULTS: 1 2 3 FIGO STAGING:

RADIO Tx: 1 2 TYPE OF RADIO 1 Tx: CH 1 2

Annexure 2: Biomedical Research Ethics Committee approval



UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

29 November 2012

Professor JS Bagratee
Department of Obstetrics and Gynaecology
School of Clinical Medicine
College of Health Science

Dear Professor Bagratee

PROTOCOL: "Clinical profile and management of women treated with endometrial adeno carinoma in Durban, South Africa." Student: Dr L Augustine, student number: 203520095 (Department of Obstetrics and Gynaecology)

I am pleased to inform you that the abovementioned study has been approved.

Please note:

- The Academic Leader: Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

for Professor JK Burns
Academic Leader School Research
School of Clinical Medicine

C Dr L Augustine

Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
Postal Address: P/Bag X3, Congella, Durban, 4013, South Africa
Telephone: +27 (0) 31 260 4745 **Facsimile:** +27 (0) 31 260 4723 **Email:** jantjies@ukzn.ac.za **Website:** www.ukzn.ac.za

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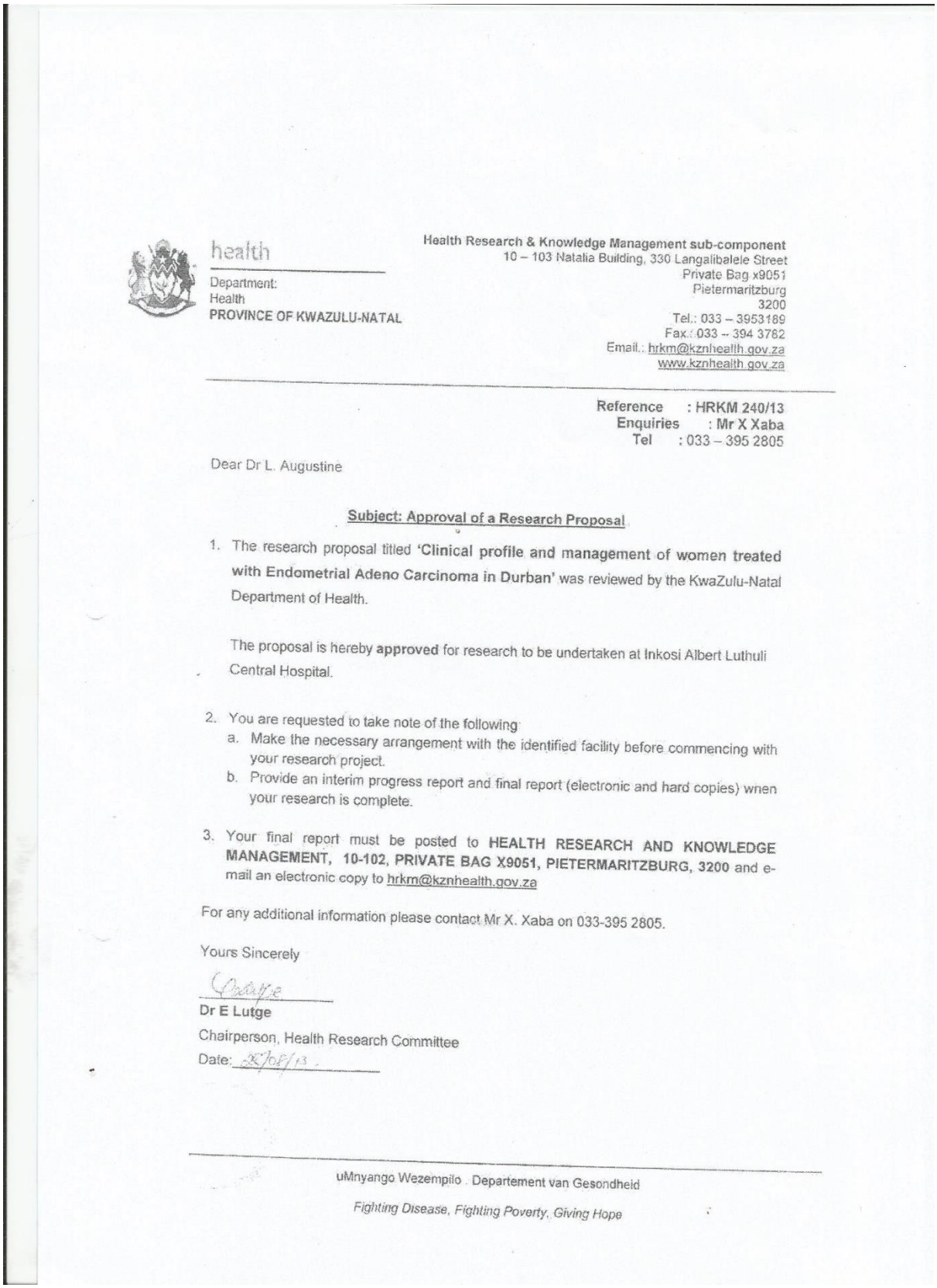
Annexure 3: Postgraduate Office approval



health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 240/13
Enquiries : Mr X Xaba
Tel : 033 – 395 2805

Dear Dr L. Augustine

Subject: Approval of a Research Proposal

1. The research proposal titled **'Clinical profile and management of women treated with Endometrial Adeno Carcinoma in Durban'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 25/08/13

uMnyango Wezempilo . Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Declaration of all funding applications / grants, please supply substantiating documentation.
5. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to **Mrs Patricia Ngwenya:** Biomedical Research Ethics Administrator, Room N40, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address: Inkosi Albert Luthuli Hosp. Investigator/s:
Principal: Dr Leon Augustine
Co-investigator:
Co-Investigator:

Signature of Chief Medical Superintendent/Hospital Manager:
Date: 2/8/2013

Site 2 address: Investigator/s
Principal:
Co-investigator:
Co-Investigator:

Signature of Chief Medical Superintendent / Hospital Manager:
Date:

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

Annexure 4: Inkosi Albert Luthuli Central Hospital approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059.
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

1 August 2013

Dr L Augustine
Department of Obstetrics and Gynaecology
IALCH

Dear Dr Augustine

Re: Research Approval: Ref No: BE313/12: Clinical profile and management of women treated with endometrial adeno carcinoma in Durban, South Africa.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg , 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

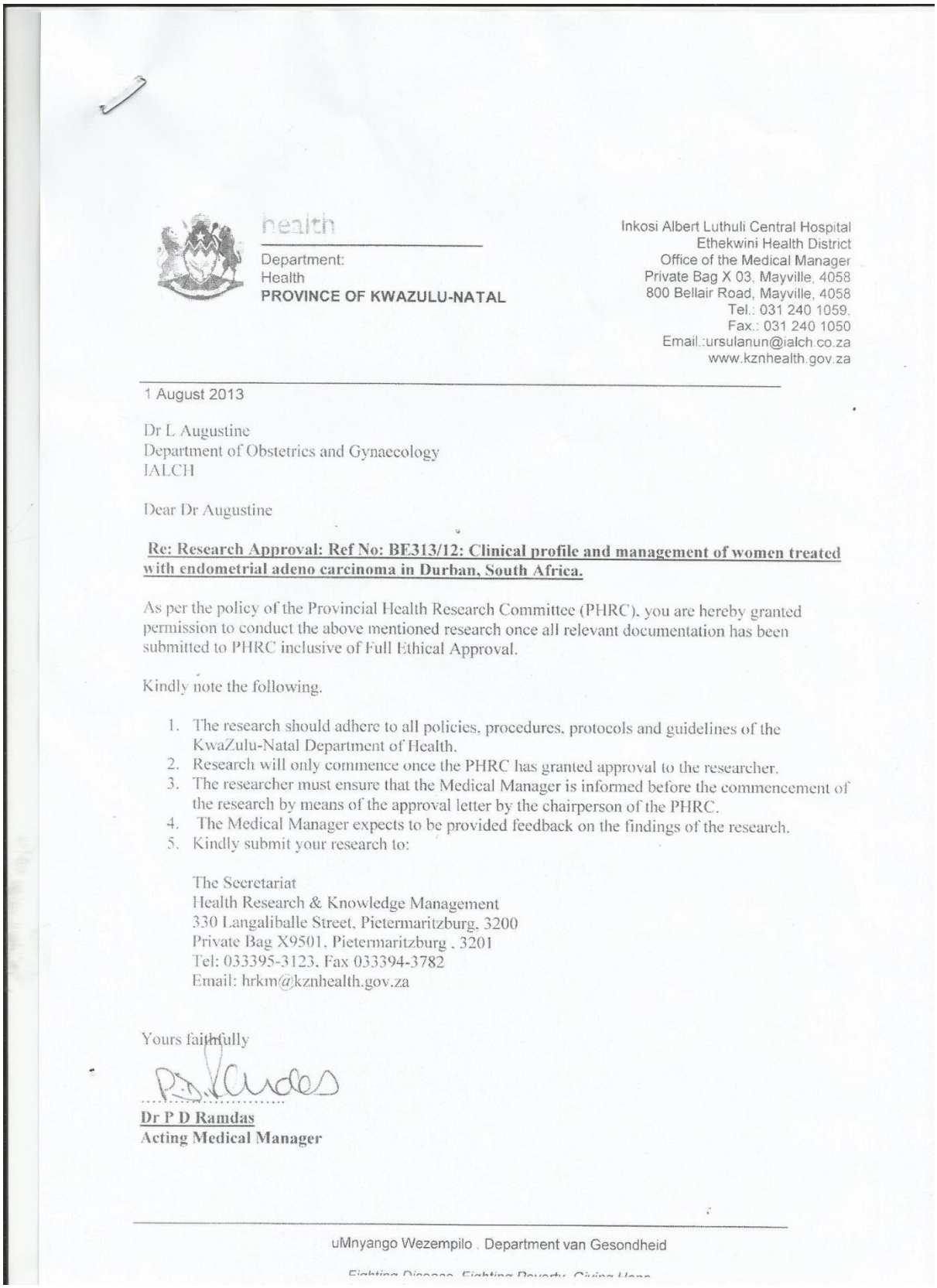
Yours faithfully

P.D. Ramdas

.....

Dr P D Ramdas
Acting Medical Manager

Annexure 5: Approval from KZN Department of Health



health

Department:
Health
PROVINCE OF KWAZULU-NATAL

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1 August 2013

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IALCH

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Yours faithfully

P.D. Ramdas

Dr P D Ramdas
Acting Medical Manager

uMnyango Wezempilo . Department van Gesondheid

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