A RETROSPECTIVE REVIEW OF UTERINE MALIGNANCIES AMONGST WOMEN PRESENTING TO THE GYNAECOLOGY ONCOLOGY CLINIC, INKOSI ALBERT LUTHULI CENTRAL HOSPITAL (IALCH).

Dr Xanti B.S. Pupuma

The thesis is submitted in part fulfilment of the requirement for the degree of **Masters in Medicine (Obstetrics and Gynaecology)** at Nelson R Mandela School of Medicine, University of KwaZulu Natal.

PLAGIARISM

DECLARATION

I.....XANTI BOSCO KUPCAM D.....declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons'data, picture, graphs or other information, unless specifically acknowledged as being sourced from other persons.

(iv) This dissertation does not contain other persons' writing, unless specifically acknowledge as being sourced from other researchers. Where other written sources have been quoted, then:

a) their words have been re written but the general information attributed to them has been referenced;

b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.

(v) Where I have reproduced a publication of which I am an author, co-author or editor, I have indicated in details which part of the publication was actually written by myself alone and have fully referenced such publications

(vi) This dissertation does not contain text, graphics or tables copied and pasted from the internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the references section.

Signed_____ Date 26. 08. 2010

Acknowledgements

I would like to acknowledge Dr M. Moodley (supervisor) from department of obstetrics and gynaecology at NRM Medical School and Miss C. Connolly, statistician from MRC, Durban. I dedicate this thesis to my wife and kids for all the time that they have spent without me.

ABSTRACT

INTRODUCTION

Cancer of the uterine corpus is the most common pelvic gynaecological malignancy in the United States of America and in most developed countries with access to sufficient health care. Approximately 95% of these malignancies are carcinomas of the endometrium with the other 5% being sarcomas. Currently there are no screening tests for cancer of the uterus in asymptomatic women.

METHODS

The study was a retrospective review of clinical records of patients managed at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, KwaZulu Natal, South Africa. Following ethical approval from the institutional ethics committee, charts of patients treated at the Inkosi Albert Luthuli Central Hospital Gynaecology-Oncology clinic between 01 June 2001 and 30 June 2006 were reviewed. Data was entered using an excel spreadsheet and then exported to Stata 9 (Stata Corp, College Station, TX) for recoding and analysis.

RESULTS

There were 118 women with uterine malignancy in the study period. Of 118 charts reviewed, data in six charts was incomplete and therefore could not be included in the study. There were 85 patients with endometrial carcinoma (75.9%) and 27 patients with uterine sarcoma (24.1%). In this study the number of white women was too small

to be compared with black women (n = 10 vs 51) but even so, African women and Indian women were associated with worse disease and outcome (only 1 White patient presented with advanced disease – EST).

CONCLUSION

The majority of patients seen at IALCH are African or Indian reflecting the demographics of the province. White patients seek medical assistance in the private sector due to better financial circumstances. Comparison between these groups is difficult but assessment of disease and disease behaviour in African and Indian patients was done and it was realised that when this group of patients presents early and appropriate management applied, the outcome is not that different from that described for white patients in other studies.

Table of contents

Pages

Uterine malignancy – Introduction 1-2

Chapter 1

I. Endometrial carcinoma

(i) Introduction 3-4

(ii) Risk Factors 4-7

(iii) Factors decreasing the risk 8-10

II. Clinical features

(i) Symptoms 10

(ii) Signs 11

III. Diagnosis and Special investigations 11-12

IV. Classification of Endometrial carcinoma 13-17

V. Staging of Endometrial carcinoma 18-19

VI. Management

(i) Surgical management

a) Abdominal hysterectomy 20-21

b) Laparoscopic hysterectomy 21-23

c) Vaginal hysterectomy 23

(ii) Postoperative Adjuvant therapy

a) Radiation therapy 24-25

b) Chemotherapy 25-26

c) Hormonal therapy 26-28

Chapter 2

I. Uterine sarcoma – Introduction 29-30

(i) Carcinosarcoma 30-31

(ii) Endometrial Stromal Tumour and Leiomyosarcoma 31-32

II. Treatment options 32-34

Chapter 3

I. The aim of the study 35

II. Methods

a) The Study design 36

III. Statistical analysis 36

Chapter 4

I. Results 37-40

Chapter 5

I. Discussion 41-45

II. Conclusion 46

Appendix 1 47-51

Appendix 2 52-55

References 57-70

1. UTERINE MALIGNANCY

Introduction

Invasive neoplasms of the female pelvic organs account for almost 15% of all cancers in women (Winter and Goseweler, 2006). Cancer of the uterine corpus is the most common pelvic gynaecological malignancy in the United States of America and in most developed countries with access to sufficient health care. Approximately 95% of these malignancies are carcinomas of the endometrium with the other 5% being sarcomas. Currently there are no screening tests for cancer of the uterus in asymptomatic women.

Endometrial cancer is primarily a disease of post menopausal women with the average age being 60 years at the time of diagnosis. Endometrial cancer is the commonest gynaecological cancer in the United States of America (USA). It ranks fourth in terms of incident cancers in women, and eighth in terms of age-adjusted mortality (Landis et al, 1999). In the United States in 1999, endometrial cancer accounted for about 6% of all incident cancers and 2% of cancer deaths in women. Endometrial cancer is the ninth most common malignancy in females. Inherited forms of this malignancy exist. Mutations in mismatch repair genes result in hereditary non-polyposis colorectal cancer, which confers a lifetime risk of bowel cancer between 60 and 80% and an endometrial cancer risk of up to 60% (Evans, 1995). Current screening involves the use of transvaginal ultrasound and endometrial sampling where indicated. Genetic

testing for mutations in the mismatch repair genes is available, and if a pathogenic change is found within a family, predictive testing becomes available for unaffected family members.

Uterine sarcomas tend to affect younger women and are more common in Black women.

Uterine sarcomas encompass leiomyosarcoma, carcinosarcoma (CS), and endometrial stromal sarcoma according to traditional classification systems. During the last 15 years, epidemiological, clinicopathogical, immunohistological, *in vitro, in vivo,* and molecular genetic research have found arguments to support the monoclonal nature of CS which points towards an endometrial origin (Ronnett et al, 2002). Recent textbooks therefore classify CS as a subtype of endometrial cancer. The literature describing the epidemiology of these tumours is sparse with the most comprehensive reports describing these tumours published in 1986 and 1995. In 1986, Harlow et al, noted an excess incidence of leiomyosarcoma and mixed mesodermal sarcoma for blacks compared with whites. However, little information was available at that time regarding survival, stage distribution, and treatment. The subsequent report by Platz and Benda (1995) acknowledged leiomyosarcoma and mixed mullerian tumours/carcinosarcomas as the most common of the sarcomas and noted that blacks with carcinosarcoma were less likely to be diagnosed with localized disease compared to whites.

CHAPTER 1

I. ENDOMETRIAL CARCINOMA

i. Introduction

Endometrial cancer occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The role of oestrogen in the development of most endometrial cancers has clearly been established. Any factor which increases exposure to unopposed oestrogen increases the risk for endometrial cancer. In the United States of America (USA), it is the most common malignancy of the female genital tract with about 39,300 new cases annually, resulting in more than 6,600 deaths (Lurain, 2002). From 1986 to 1990, approximately 19% of US Surveillance, Epidemiology and End Results (SEER) Program cases were diagnosed in women less than 55 years of age. However, the age-specific incidence (per 100,000) peaked at 70-74 years, which was 2.85 times the rate reported at 50 to 54 years (Schottenfeld, 1995). The incidence of endometrial cancer in women under 50 years was 2.19 times higher in the United States. African-American women with endometrial cancer have more advanced disease and less favourable tumour grade than do White women (Hill et al, 1995 and Liu et al, 1995). Aziz et al (1993) also found Black patients to have poorer survival rate when compared to White patients. They also presented with more advanced disease than White females. Aziz et al (1993) reviewed 290 patients between 1975 and 1990 who presented at the Health Science Centre at Brooklyn and Kings County Hospital Centre of which 47.2% were black and 46.9% were white. Of the patients who presented in stage III disease, 88.89% were black and 11.1% were

white (p = 0.034), and with grade III disease, 70.5% were black and 29.5% were white (p = 0.008). Seventy two percent of positive lymph nodes were in black patients compared to the 28% in white patients (p = 0.01). The overall ten-year corrected survival for white and black patients was 72% and 40%, respectively (p = 0.0003). Hill et al (1995) reported that although the incidence of uterine carcinoma is lower among African-American women compared with white women, the mortality rates are higher for African-American patients.

ii. Risk factors

Majority of risk factors and medical conditions associated with endometrial cancer are related directly or indirectly to the levels and metabolic effects of the reproductive hormones, namely oestrogen and progestogens (Schottenfeld, 1995). These risk factors include:

- Parity. Nulliparous women have 2 to 3 times the risk of parous patients. It was initially observed in England and Wales that single women and married women without children had higher death rates from uterine corpus cancer than married parous women (Brinton et al, 1992). It is not certain whether spontaneous miscarriages influence a woman's risk of endometrial cancer but an increased risk associated with induced abortions has been reported (McPherson et al, 1996)

- Late menopause (occurring after 52 years) is associated with increased risk for endometrial cancer 2.4 times compared with that in women whose menopause occurred before 49 years of age. Endometrial cancer risk is also increased in women with long and irregular menstrual cycles (Henderson et al, 1983). Most studies have found that early age at menarche (generally defined as before age 11 or 12 years) is associated with 1.5-4 fold increase in risk of endometrial cancer (Elwood et al, 1997 and Brinton et al, 1992).

- Obesity is associated with a 3 to 10 times increased risk for endometrial cancer, with some studies finding significant increasing risk with increasing measures of central adiposity, after adjustments for body mass index (BMI) (Swanson et al, 1993). Post-menopausal obese women are known to have higher endogenous oestrogens than lean women due to the aromatization of androstenedione in adipose tissue (Enriori and Reforzo, 1984). Obesity is also associated with reduced levels of sex hormone-binding globulin, which would further increase the amount of bioavailable oestrogen (Davidson et al, 1981).

- Hormone Replacement Therapy (HRT) without progestins increases the risk for endometrial cancer 4 to 8 times. By far the most consistent, and possibly the most controversial, factor associated with endometrial cancer is use of oestrogen replacement therapy. An increase in the incidence of endometrial cancer in the 1970s followed a marked increase in the sales of oestrogen for treatment of menopausal symptoms in the United States between 1962 and 1975. (This increase in incidence was not paralleled by an increase in mortality from the disease) As a corollary, when rates of prescription of

oestrogens began to decline in the late 1970s, a decrease in the incidence of endometrial cancer followed. Administration of cyclic progesterone (for at least 10 days of each treatment cycle) appears to mitigate the continuous mitotic stimulation of the endometrium by unopposed oestrogen therapy (Weiderpass et al, 1999a), and its incomplete shedding. Progesterone antagonizes the effect of oestrogen by decreasing oestrogen receptors and increasing the activity of enzymes that metabolize oestradiol to less potent metabolites.

- Diabetes mellitus is associated with increased risk of 1.3 to 2.8 times, and other conditions like Hypertension and Hypothyroidism have been associated with endometrial cancer, but a causal relationship has not been confirmed (Lurain, 2002). One possible explanation is that these conditions are simply markers of obesity (Jung, 1997). Some have found that both associations became less consistent after adjustment for body mass, others that only the association with diabetes persisted (Brinton et al, 1992), although others have found both to persist after adjustment not only for body mass but also for other confounding factors, including parity, oestrogen replacement therapy use and smoking status (Elwood et al, 1997).It has also been suggested that the increased risk associated with diabetes and hypertension may be restricted to obese or overweight women

- Family history of endometrial carcinoma is found in 15% of cases (du Toit, 2001). Very little research has examined the question of whether women with

a family history of endometrial cancer is at increased risk of the disease. Some have observed a small (50%) increase in risk associated with a family history of

endometrial cancer (Parazzini et al, 1994). A genetic predisposition to the development of (non- polyposis) colon cancer, pancreatic, ovarian and breast carcinoma occurs in an autosomal condition, the Lynch Type II syndrome.

- The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia. Kurman et al (1985) found that progression to carcinoma occurred in 1% of patients with simple hyperplasia, 3% of patients with complex hyperplasia, 8% of patients with atypical simple hyperplasia, and 29% of patients with atypical complex hyperplasia.

- Endogenous oestrogen; women with polycystic ovarian syndrome (PCOS) are anovulatory and are thus at increased risk of endometrial carcinoma. Ovarian granulosa cell tumours are associated with endometrial hyperplasia and carcinoma due to their oestrogenic effects on the endometrium. These conditions appear to be especially linked to the occurrence of endometrial cancer in young women. The diagnosis of polycystic ovarian syndrome has been made in up to 30% of cases with endometrial cancer in selected groups of pre-menopausal women.

iii. Factors decreasing the risk

- Grand multiparity and Intrauterine Device

With intense placental production of progestagens, pregnancy protects against endometrial cancer. Hinkula et al in 2002 and Chubak et al in 2004 reported that nulliparity is a risk factor that is more important if infertility is also present whereas grand multiparity protects against endometrial carcinoma . The use of an intrauterine device and tubal ligation have also been associated with a lower risk (Hubacher and Grimes, 2004). Whether a Mirena provides any further protection from endometrial carcinoma is unclear (Suvanto-Luukkonen et al, 1995).

- **Smoking**

A number of studies have found that women who have ever smoked are at reduced risk of endometrial cancer, although several have suggested that this association is restricted to post-menopausal women (Stockwell and Lynman, 1987 and Parazzini et al, 1994). The reduced risk of endometrial cancer in smokers even controversial is thought to provide further evidence of an anti-oestrogenic effect of smoking. The other arguement is that rather than affecting risk of endometrial cancer by reducing oestrogen, smoking may act by increasing levels of circulating androgen (Austin et al, 1993). Cigarette smoking has also been considered as a possible effect modifier of the associations between other factors, such as oestrogen use and obesity and endometrial cancer. Some studies have found the protective effect of smoking to be greater among postmenopausal women using oestrogen rather than the ones not using it, although

other studies have found no significant interaction between smoking and oestrogen replacement therapy (Levi et al, 1993).

- **Oral-contraceptive use**

That use of the combined oral contraceptive pill (oestrogen plus progestogen) reduces the risk of endometrial cancer and has been reported consistently. Long-term use of combined oral contraceptives appears to reduce the risk further, and the protective effect lasts for 20 or more years after discontinuation. Results of some studies (but not all) suggest that the protective effect of the combined oral contraceptive pill does not depend on the dose of the progestogen: the risk is similar whether the progestogen content is high or low (Weiderpass et al, 1999b and Parslov et al, 2000).

- **Physical activity**

The close relationships between diet, physical activity and body mass have made it difficult to assess the independent risks of the three on endometrial cancer. Whether physical activity plays a role via its association with obesity or whether it has an independent effect on risk of endometrial cancer is not clear. The only thing clear from the literature is that increased levels of physical activity reduce serum oestrogen levels (Cauley, 1989).

- **Diet of some phyto-oestrogens**

There have been suggestions of a protective effect of increasing phyto-oestrogen consumption on risk of endometrial cancer among postmenopausal women, even if

they are obese (Goodman et al, 1997 and Xu et al, 2004). The effect of eating a diet rich in soy throughout a lifetime cannot be compared with use of soy extracts given after the menopause. Unfer et al in 2004 reported that a daily intake of 150 mg isoflavones consisting of genistein (40 – 45%), daidzein (40 – 45%), and glycitein (10 – 20%), for 5 years has been associated with endometrial hyperplasia. Alcohol use is associated with raised oestrogen concentrations. Epidemiological studies, however, do not support a positive association between alcohol use and endometrial cancer as shown for breast cancer (Bandera et al, 2003).

II. CLINICAL FEATURES

i. Symptoms

About 90% of women with endometrial carcinoma present with vaginal bleeding or discharge as their only presenting complaint. Less than 5% of women diagnosed with endometrial cancer are asymptomatic (Lurain, 2002). In the absence of symptoms, endometrial cancer is usually detected as the result of investigation of abnormal Papanicolaou smear results, or an incidental finding post hysterectomy or evaluation of an abnormal finding on a pelvic ultrasound or computed tomography (CT) scan obtained for an unrelated reason (Dubeshter, et al, 1991). Abnormal peri-menopausal and post-menopausal bleeding should always be taken seriously and be properly investigated, no matter how minimal. Vaginal discharge due to secondary infection of the tumour or a pyometra may be the presenting complaint and pain is usually a late presentation of the disease and is associated with metastatic spread (du Toit, 2001).

ii. Signs

Physical examination seldom reveals any evidence of endometrial carcinoma, although obesity and hypertension are commonly associated constitutional factors. Lymph nodes should be palpated, especially the supraclavicular and inguinal lymph nodes. Abdominal examination is usually unremarkable except in advanced cases in which ascites, hepatic or omental metastases may be palpable. Gynaecological examination usually does not reveal much, but the introitus and suburethral area should be assessed carefully.

III. DIAGNOSIS AND SPECIAL INVESTIGATIONS

- Out-patient endometrial aspiration biopsy is the accepted first step in evaluating a patient with abnormal uterine bleeding or suspected endometrial pathology (Chambers and Chambers, 1992). This usually follows transvaginal ultrasound assessment of the endometrium (looking for thickened endometrium). Endometrial cancer is mostly diagnosed histologically from endometrial tissue obtained with miniature endometrial biopsy devices (generally based on the plastic disposable Pipelle de Cornier prototype) (Amant et al, 2005). A meta-analysis of the value of Pipelle biopsy for the diagnosis of atypical hyperplasia or endometrial cancer calculated sensitivity of 81–99% and specificity of about 98% and this was

further confirmed by a systematic quantitative review of 11 published studies done by Dijkhuizen et al in 2000 and Clark et al in 2002.

- Hysteroscopy and dilation and curettage should be reserved for situations in which cervical stenosis or patient tolerance does not permit adequate evaluation by aspiration biopsy; bleeding recurs after a negative endometrial biopsy, or the specimen obtained is inadequate to explain the abnormal bleeding (Gimpleson and Rappold, 1988).

- Transvaginal ultrasound is useful for evaluating abnormal uterine bleeding and selecting patients for additional testing (Bourne et al, 1991). The finding of an endometrial thickness greater than 4 mm, a polypoid endometrial mass, or a collection of fluid within the uterus requires further evaluation (Lurain, 2002).

- A pap smear is an unreliable diagnosis test because only 30 – 50% of patients with endometrial cancer have abnormal Pap test results (Zucker et al, 1985).

- A chest x-ray, abdominal ultrasound, full blood count and serum chemistry (includes renal and liver function test) are investigations performed routinely in some centres while in others they are done as part of pre-treatment evaluation.

IV. CLASSIFICATION OF ENDOMETRIAL CARCINOMAS (Gordon and Ireland, 1994)

• Endometroid adenocarcinoma		80%
	Usual type	> 50%
	Variants - Villoglandular or papillary	2%
	- Secretory	1%
	- With squamous differentiation	15-25%
• Mucinous carcinoma		5%
• Papillary serous carcinoma		3-4%
• Clear cell carcinoma		5%
• Squamous carcinoma		1-2%
• Undifferentiated carcinoma		<1%
• Mixed carcinoma		<1%

a) Endometriod adenocarcinoma

Accounts for about 80% of endometrial carcinoma (Gordon and Ireland, 1994). These tumours are composed of glands that resemble normal endometrial glands. They have columnar cells with basally oriented nuclei, little or no intracytoplasmic mucin, and smooth intraluminal surfaces. About 15-25% of endometriod carcinomas have areas of squamous differentiation. They are then known as endometrial carcinoma with squamous differentiation and their behaviour is largely dependent on the grade of the glandular component (Zaino et al, 1991). A villoglandular configuration is present in about 2% of endometriod carcinomas (Sutton et al, 1987). The cells are arranged along fibro vascular stalks, giving a papillary appearance but maintaining the characteristics of endometriod cells. Secretory carcinoma is a rare variant of endometriod carcinoma that accounts for about 1% of cases (Tobon and Warkins, 1985). It occurs mostly in women in their early postmenopausal years and is associated with an excellent prognosis. These tumours are composed of well differentiated glands with intracytoplasmic vacuoles similar to early secretory endometrium.

Histological grading applies only to endometriod carcinomas. Serous and clear-cell carcinomas are classed as high grade by definition. According to the system of the International Federation of Gynaecology and Obstetrics (FIGO), an endometrioid carcinoma of grade 1 consists of well-formed glands, with no more than 5% solid non-squamous areas (areas of squamous differentiation are not deemed to be solid tumour growth) (Creasman, 1987). Carcinomas of grade 2 consist of 6-50% and those of grade 3 of more than 50% solid non-squamous areas (Zaino et al, 1995). The tumour is upgraded from grade 1 to 2, or from grade 2 to 3, if there is striking cytological atypia. Most endometroid carcinomas are well to moderately differentiated and arise on a background of endometrial hyperplasia. These tumours,

also known as type 1 (low-grade) endometrial carcinomas, have a favourable prognosis (Bokhman, 1983). They are associated with long-duration unopposed oestrogenic stimulation. About 10% of endometrial cancers are type 2 (high-grade) lesions. Women with such tumours are at high risk of relapse and metastatic disease. These tumours are not oestrogen driven, and most are associated with endometrial atrophy; surgery is commonly followed by adjuvant therapy. The histological type is either poorly differentiated endometrioid or non-endometrioid.

b) Mucinous Carcinoma

Melhem and Tobon in 1987 reported that about 5% of endometrial carcinomas have a predominantly mucinous pattern in which more than half of the tumour is composed of cells with intracytoplasmic mucin. Their behaviour is similar to that of endometroid carcinoma and the prognosis is good.

c) Uterine Papillary Serous Carcinoma (UPSC)

Uterine papillary serous carcinoma (UPSC) is an uncommon aggressive type of endometrioid adenocarcinoma that was delineated by Hendrickson et al in 1982 as a clinico-pathological entity distinct from endometrioid carcinoma. Attention was drawn primarily to the presence of psammoma bodies and predominantly papillary architecture, although solid areas can be present focally in the dilation and curettage material (D & C).Uterine Papillary Serous Carcinoma is an aggressive variant of endometrial cancer found in 5% of cases. A higher incidence of deep myometrial

invasion, lymph-vascular space involvement, lymph node metastases, extra uterine disease, and positive peritoneal cytology and implants is characteristic. Even with surgical stage I cancer, the 5-year survival rate is 60%. Uterine Papillary Serous Carcinoma histologically resembles papillary serous carcinoma of the ovary. Although adjuvant chemotherapy is helpful, UPSC does not have the same duration of response to cytotoxic agents (eg, paclitaxel, carboplatin) as its ovarian counterpart. The first report on the use of paclitaxel in UPSC was a case report by Resnik and Taxy (1996) who described a dramatic response in an advanced UPSC tumour after three cycles of paclitaxel and carboplatinum given as neoadjuvant therapy. Zanotti et al (1999) treated 24 patients with UPSC with paclitaxel (175 mg/m^2) alone or paclitaxel (175 mg/m^2) combined with carboplatin area under curve (AUC = 5) or cisplatin (75 mg/m^2). Eighteen patients received the regimens in the adjuvant setting. Eleven patients received one or more courses of this combination for recurrent disease. A median progression-free survival (PFS) of 30 months (range 8-61 months) was seen in patients treated in the adjuvant setting. An objective response indicated by normalisation of CA 125 was seen in eight of nine patients treated for residual disease after initial surgery (median PFS of 13 months, range 5-38 months), while an objective response was seen in seven out of eleven patients with recurrent disease (median PFS of 9 months, range 4-18 months).Often, elements of clear cell carcinoma are associated with UPSC. Widespread metastases and death can occur even in those cases in which the tumour is confined to the endometrium or to an endometrioid polyp.

d) Clear Cell Carcinoma

The concept of clear-cell carcinoma as being of mesonephric origin and designated as 'mesonephroma' was introduced in 1939 by Schiller to describe a subtype of ovarian tumour which resembles renal carcinoma and tumours originating from the mesonephric duct system. Scully and Barlow (1967) related the origin of the latter group of tumours to the Mullerian epithelium rather than the mesonephros and proposed the descriptive term `clear-cell carcinoma' (CCC). The prognostic implication of CCC was not recognized until 1976 when Kurman and Scully (1976) reported a series of 21 cases with an unfavourable clinical course. In the early literature, survival for CCC was usually given for clinically staged patients with an overall survival ranging from 21 to 60%. Abeler and Kjostard (1996) in the largest single institution study from The Norwegian Radium Hospital (NRH) (181 patients) demonstrated a 5 and 10 year actuarial disease-free survival rate of 43 and 39% respectively (for all stages). The 5-year survival for pathological stage I CCC of 54% and for stage II of 27% was lower than that reported by Carcangiu and Chambers (1992) of 72% and 59% respectively. These tumours classically occur in older women and are very aggressive types of endometrial cancer.

e) Squamous Carcinoma

This is a rare type. This tumour has a poor prognosis, with estimated 36% survival rate in patients with clinical stage I disease.

V. STAGING OF ENDOMETRIAL CARCINOMA

Since 1998, endometrial cancer has been staged surgically. Prior to this, the disease was staged clinically, since almost all patients were treated with pre-operative radiotherapy, only information gained at initial dilation and curettage could be reliably used for prognostic purposes, all information obtained by examining the uterine specimen having been affected to some degree by the radiotherapy (Lawton, 2003).

International Federation of Gynaecology and Obstetrics (FIGO) (1988)

Staging for Carcinoma of the Corpus Uteri	
Stage*	Description
IA (G1, G2, G3)	Tumor limited to endometrium
IB (G1, G2, G3)	Invasion of less than one half of the myometrium
IC (G1, G2, G3)	Invasion of more than one half of the myometrium
IIA (G1, G2, G3)	Endocervical gland involvement
IIB (G1, G2, G3)	Cervical stromal involvement
IIIA (G1, G2, G3)	Invasion of serosa and/or adnexa and/or positive peritoneal cytologic results
IIIB (G1, G2, G3)	Metastases to vagina
IIIC (G1, G2, G3)	Metastases to pelvic and/or para-aortic lymph nodes

IVA (G1, G2, G3)	Invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes

*Carcinoma of the corpus is graded (G) according to the degree of histological differentiation: G1 = 5 percent or less of a solid growth pattern; G2 = 6 to 50 percent of a solid growth pattern; G3 = more than 50 percent of a solid growth pattern.

From International Federation of Gynecology and Obstetrics. Annual report on the results of treatment in gynaecologic cancer (Sherphard, 1989).

VI. MANAGEMENT

i. Surgical management

a) Abdominal Hysterectomy

Type 1 endometrial cancer spreads primarily via the lymphatic system and is often limited to pelvic nodes. Total abdominal hysterectomy and bilateral salpingo-oophrectomy are the primary operative procedures for carcinoma of the endometrium. Most cases of endometrial cancer are stage 1 disease, which means that the primary tumour is confined to the corpus and can be excised entirely, with the myometrial thickness providing a barrier to spread to surrounding pelvic structures. Using this conservative approach, tumours are then divided into low-risk and high-risk to select the need for adjuvant radiotherapy which is given to irradiate pelvic nodes in case of nodal involvement as well as the vault where there is a risk of recurrence. Some gynaecological oncologists advocate slicing open the uterus immediately following its removal in order to eyeball the degree of myometrial invasion as a means of determining whether to proceed to lymphadenectomy. A recent prospective study by Franchi et al (2000) indicated that visual inspection correlated with microscopic assessment in 85% of cases. However, the sensitivity of determining >50% was lower at 72%. Whilst some would support this technique, it is not accurate enough to be recommended as a routine. Kilgore et al (1995) suggested that lymphadenectomy may be of some therapeutic benefit in their cohort study. They reviewed over 600 patients of whom, 212 had multiple site pelvic node sampling of which, 205 had limited node sampling and 208 had no node sampling at all. All patients had a hysterectomy and bilateral salpingo-oophrectomy with peritoneal cytology. They concluded that the overall survival rate for the patients who had multiple node sampling was better than patients who had none. Whether lymphadenectomy is curative in endometrial cancer remains controversial. Recent findings suggested that it was curative in women with

grade-3 endometrial cancer, when more than 11 nodes were removed (Cragun et al, 2005). Furthermore, in a study from Scotland including 703 patients with endometrial cancer, deficient staging was associated with poorer survival (Crawford et al, 2002). The first multicentre randomised trial to investigate the curative value of standard lymphadenectomy for endometrial cancer of stages 1 and 2 is the recently closed UK MRC ASTEC trial. Less aggressive surgical approach has been proposed by Mariani et al (2001). In their series, pelvic lymphadenectomy and radiotherapy were abandoned in patients with endometriod cancer of grade 1 or 2 with greatest surface dimension of 2 cm or less, myometrial invasion of 50% or less, and no intraoperative evidence of macroscopic disease. Among 328 patients, 5-year overall cancer-related survival was 97% and recurrence-free survival 96%.

b) Laparoscopic surgery

Although the results of randomised trials are still lacking, in experienced hands, laparoscopy-assisted vaginal hysterectomy is feasible when operating for endometrial cancer. (Yu et al, 2005). It also presents the opportunity to take fluid for cytology, peritoneal biopsy samples, lymph nodes, and omentum samples in a single procedure. Amant et al (2005) compared clinical outcomes in women who had surgical staging for early-stage endometrial cancer by laparoscopy (n=80) or by laparotomy (n=105) during the same period. Exclusion criteria for laparoscopy included poor uterine descensus, largest uterine diameter from ultrasonography of more than 10 cm, Body Mass Index (BMI) more than 35 kg/m^2, and history of previous laparotomy or pelvic radiotherapy. The mean age (62 *vs* 66 years; p=0.012) and BMI (26 *vs* 31 kg/m^2;

p<0.001) were lower in the laparoscopy group than in the laparotomy group. Although the operation was slightly longer for patients in the laparoscopy group (169 *vs* 152 min; p=0.063), they had less blood loss (344 *vs* 505 ml; p=0·0002) and a shorter hospital stay (5.6 *vs* 10.1 days; p<0.001). After follow-up of 55 months, multivariate analysis showed no difference in progression-free survival (odds ratio 0.89; p=0.52) or overall survival (0.96; p=0.63). They concluded that due to absence of randomised trials on this issue, laparoscopy is a valuable alternative to laparotomy in selected patients. Manipulation of tumour, including macroscopically involved lymph nodes, should be avoided to prevent the rare occurrence of port-site metastasis. Furthermore, the use of an intrauterine manipulator should be avoided, since it results in a high frequency of positive peritoneal cytology and might contribute to vaginal-cuff recurrence (Sonoda et al, 2001 and Schneider 2004). Where macroscopic extra uterine disease or macroscopically positive pelvic lymph nodes are found conversion of the incision into a midline is recommended. Maylard incision or metal transabdominal traction sutures (Ventrofil) for midline incisions are frequently used in obese women with the aim to decrease wound morbidity.

Since 1992, there have been several reports that have documented the feasibility of laparoscopic-assisted vaginal hysterectomy with bilateral salpingo-oophrectomy and laparoscopic retroperitoneal lymph node sampling for staging and treatment of patients with endometrial cancer (Boike et al, 1994 and Gemignani et al, 1999). Holub et al, (2002) illustrated that laparoscopic assisted surgical staging of endometrial cancer is safe as an open procedure. The laparoscopic procedure may also be considered for endometrial malignancy which typically occurs in obese and elderly, high risk women. Holub et al, (2002) compared 177 patients who had laparoscopic surgery with 44 patients who had open surgery and followed them for 33.6 months

and found no difference with respect to recurrence or survival rate. The only disadvantage was that the laparoscopic approach took longer than open surgery.

c) Vaginal Hysterectomy

Vaginal hysterectomy may be considered for selected patients who are extremely obese and have a poor medical status, or for patients with extensive uterovaginal prolapse (Lurain, 2002). Although these patients will tolerate vaginal surgery better, it may be difficult to assess the extent of the disease in the pelvis and abdomen. The disadvantage is that bilateral salpingo-oophrectomy is technically difficult and lymph node sampling cannot be performed. Vaginal hysterectomy is, therefore, particularly suitable for patients who are at low risk for extra uterine spread disease. Chan et al, (2001) found a survival rate of 94% in patients with stage I disease with/ without postoperative radiotherapy. Vaginal hysterectomy is clearly preferable to radiation therapy alone, but generally should be reserved for specific patients. Peters et al (1983) report of 56 patients with stage I disease treated by vaginal hysterectomy, with or without adjunctive therapy, showed a 94% 5 year survival rate. The update of this series by Lelle et al (1994) added four additional patients. The crude survival rate at 5 and 10 years was 91.1% and 87.1%, respectively, with only one patient dying of cancer 6 years after primary treatment.

ii. Postoperative Adjuvant Therapy

a) Radiation therapy

Primary surgery followed by individualized radiation therapy has become the most widely accepted treatment for early-stage endometrial cancer (Lurain, 2002). Several series have demonstrated radiotherapy to be an effective treatment for patients with inoperable endometrial cancer (Kupelian et al, 1993 and Lehoczky et al, 1991). Creutzberg et al (2000) showed that the 5-year survival rate of patients who had radiotherapy postoperatively was not different from the group who had radiotherapy alone (85% vs. 81%). They randomized their patients identified as medium-risk (grade 1 tumour with >50% invasion, grade 2 tumours with any degree of invasion and grade 3 with superficial invasion) into Total Abdominal Hysterectomy (TAH) and Bilateral Salpingo-ophorectomy (BSO) alone or surgery plus postoperative radiotherapy. The decision to treat a patient who has endometrial cancer with radiation alone must involve a careful analysis of the relative risks and benefits of surgery. When radiotherapy is recommended in addition to surgery in contemporary management of endometrial cancer it is most often given as post-operative adjuvant therapy. In the past, pre-operative radiation was more frequently used but this approach has lost favour due to delay in definitive treatment, potential loss of pathological information and inability to tailor adjuvant therapy appropriately to specific surgico-pathological findings. Kucera et al, (1990) reported on a large series of 605 patients who were treated with primary TAH and BSO, of which 10% underwent retroperitoneal lymphadenectomy. All patients received vaginal brachytherapy. However, external beam pelvic radiation was given only to 229 selected patients who had more deeply invasive and higher grade tumours (grade 1 and 2/3 myometrial invasion, or grade 2 or 3 and 1/3 invasion). Using this treatment paradigm, the authors noted that survival in patients with adverse intrauterine features was similar to that in more favourable patients, with 5 year survival rates

approximating 90% in both groups. The results suggested that the addition of pelvic radiotherapy was able to compensate for the otherwise poorer outcomes expected for patients with unfavourable intrauterine pathological findings. Contributing to the controversy over the role of adjuvant radiation therapy is the variability with which different investigators characterize overall patient prognosis. It is clear that there exists a large proportion of endometrial cancer patients who enjoy very favourable prognosis and for whom no adjuvant therapy is warranted. Inclusion of such low-risk cases (stage 1, grade 1 or 2) in clinical studies of adjuvant radiotherapy can only diminish the likelihood of observing potential benefit in patients with higher-risk tumours (>stage 1c and grade 3). Well designed prospective studies are needed to evaluate the role of adjuvant radiation in patients with intermediate and high-risk disease.

b) Chemotherapy

Cytotoxic chemotherapy has no proven role in the treatment of early-stage disease but is used as a palliative treatment in patients with advanced disease. High cure rates by surgery and radiotherapy have precluded much interest in adjuvant chemotherapy in the majority of patients. Chemotherapy has been found to be useful in the management of uterine papillary serous carcinoma (2-10% of all endometrial cancers) (Price et al, 1993). Price et al (1993) used cisplatin, doxorubicin and cyclophosphamide in 19 patients radically operated on without any residual tumour. Eight stage I patients were alive without evidence of disease after a median follow up of 24 months. Of the remaining 11 patients who had extrauterine disease at diagnosis, eight were dead of disease at a median of 14 months. Chemotherapy has not been

shown to be beneficial as far as recurrence of disease is concerned and no better 5 year survival (Morrow et al, 1990 and Burke et al, 1994). Only five randomized control trials of non-hormonal combination chemotherapy in advanced disease have been reported and just two have been published in peer-reviewed journals (Flemming et al, 2000 and Aapro et al, 1994). There are only three published randomized trials of chemotherapy in combination with hormonal therapy (Ayoub et al, 1988 and Cohen et al, 1984). Because of this lack of properly researched data treatment decisions are therefore made largely on the results of small phase II trials. In the current era of evidence-based medicine, this fact makes such decisions difficult. However appropriate use of systemic chemotherapy in selected patients with advanced or recurrent disease appears justified and may result in a palliative benefit. The most active single agents in clinical trials are doxorubicin, cisplatin, carboplatin, paclitaxel, epirubicin and ifosfamide. Use of combination regimens produces substantial response rates in phase II and III clinical trials. However, these high responses rates do not appear to translate into dramatic improvements in survival and overall median survival remains short (7-10 months). Until more concrete evidence becomes available the current approach as far as use of chemotherapy is concerned will continue.

c) Hormonal therapy

The profound effects of progesterone on the normal endometrium and the inherent hormonal sensitivity of this tissue led to the concept that progestins may be useful in the treatment of endometrial cancer. Factors predicting a favourable response to progestins included a long hiatus between primary therapy and the appearance of metastasis, a histologically well-differentiated endometrial adenocarcinoma, and a pulmonary site of metastasis. In favourable cases, pulmonary metastases regressed within 2 months of the initiation of therapy and disappeared by 4 to 6 months. Responsive osteolytic lesions calcified, resulting in symptomatic relief of pain and disability although standard therapy for endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy with appropriate staging, selected patients have been treated with progestational agents as primary therapy in an attempt to preserve childbearing potential. Farhi et al (1986) described ten cases of endometrial cancer arising in women under the age of 25. The slides were reviewed by at least two pathologists in order to distinguish these cases from adenomatous/atypical hyperplasia. Seven of the ten patients demonstrated the clinical characteristics of women with polycystic ovarian syndrome. Nine of the tumours were well-differentiated endometrioid adenocarcinomas and were limited to the endometrium. In one case, a moderately-differentiated adenosquamous carcinoma involved an ovary and the pelvic wall. In five cases, progestins were used as primary therapy; three of the patients had no further evidence of tumour on repeat endometrial biopsy. One of the three patients successfully treated with progestins subsequently delivered two term pregnancies.

Lawton (2003) prescribed hormonal therapy to patients after the diagnosis of endometrial cancer (i.e. before hysterectomy) and to almost all patients after surgery

either in an immediate adjuvant setting or at relapses. Patients with that were found to have positive for estrogen and progesterone receptors responded best to progestin therapy. Among 115 patients with advanced endometrial cancer who were treated with progestin's, 75% (42 of 56 patients) of those with detectable progesterone receptors in their tumours before treatment responded, compared to only 7% without detectable progesterone receptors (4 of 59 patients) (Kauppila, 1989). A receptor-poor status may predict not only poor response to progestins but also a better response to cytotoxic chemotherapy. Tamoxifen is a triphenylethylene derivative similar to diethylstilbestrol. The citrate salt of the trans isomer is used clinically because of its increased affinity for the oestrogen receptor. The customary dosage is 20 mg a day, and the drug is readily absorbed after oral administration. The `anti-oestrogen' tamoxifen is, in reality, the first selective oestrogen receptor modulator (SERM), a new category of therapeutic agents which mimic the effect of oestrogens in some tissues, but act as oestrogen antagonists in others. Based on prior experience with breast cancer, tamoxifen, either as a single agent or in combination with other hormones, has been used in the treatment of advanced and recurrent endometrial carcinoma. These studies were initiated at a time the agonist action of tamoxifen in the endometrium was not yet appreciated. There are few studies done to date and all show no response to tamoxifen. As a result, it is unlikely that patients with advanced or recurrent endometrial cancer unresponsive to progestational agents will experience a response to tamoxifen as a single agent.

CHAPTER 2:

I. UTERINE SARCOMA

i. Introduction

Uterine sarcomas are relatively rare tumours of mesodermal origin. They constitute 2% to 6% of uterine malignancies (Harlow et al, 1986). There is considerable evidence for a higher incidence of uterine sarcomas in black women when compared to white women (Amant et al, 2005). The literature describing the epidemiology of these tumours is sparse; with the most comprehensive reports describing these tumours published in 1986 and 1995. In 1986, Harlow et al. noted an excess incidence of leiomyosarcoma and mixed mesodermal sarcoma for blacks compared with whites; however, little information was available at that time regarding survival, stage distribution, and treatment. The subsequent report by Platz and Benda (1995) acknowledged leiomyosarcoma and mixed mullerian tumours/carcinosarcoma as the most common of the sarcomas and noted that blacks with carcinosarcoma were less likely to be diagnosed with localized disease compared to whites. In the United States, incidence rates for malignant tumours of the uterine corpus are lower among black women than among white women whereas the mortality rates are higher (Sherman and Devesa, 2003). Black women with carcinosarcoma were less likely to present with stage I disease than white women (Brooks et al, 2004). The risk for uterine sarcoma is higher in women with a body mass index >27, one year before diagnosis and lower in cigarette smokers, this indicates a possible link to estrogen metabolism. Malignant Mixed Mullerian Tumours (MMMT) or Carcinosarcoma almost always occur after menopause, at a median age of 62 years. These tumours are usually found in association with other conditions such as obesity, diabetes mellitus, and

hypertension. Uterine sarcomas encompass leiomyosarcoma, carcinosarcoma (CS), and endometrial stromal sarcoma (EST).

i Carcinosarcoma

The biphasic cellular population found in carcinosarcoma entered the sphere of interest of many researchers, who focused on the question whether this tumour originated from one (monoclonal theory) or two cell populations. A wide spectrum of methods has been elaborated to answer this question. During the last 15 years, epidemiological, clinic-pathogical, immuno-histological, *in vitro* and *in vivo*, and molecular genetics research have found arguments to support the monoclonal nature of carcinosarcoma that pointed towards an endometrial origin. Recent textbooks therefore classify carcinosarcoma as a subtype of endometrial cancer as reported by Ronnett et al in 2002. Consequently, the designation endometrial carcinosarcoma corresponds best to its tissue origin and should be used instead of uterine carcinosarcoma. Amant et al (2005) found carcinosarcoma to present more with bleeding than other symptoms and that it had more metastatic potential when compared with other sarcomas. Carcinosarcomas or homologous malignant mixed müllerian tumours (MMMT) typically have an endometrioid carcinoma, usually a higher grade, and an undifferentiated spindle cell sarcoma. The sarcomatous portion of the tumour may exhibit an ESS pattern, if differentiated. Malignant Mixed Mullerian tumours are termed heterologous only if identifiable extra uterine histology is demonstrated. Malignant Mixed Mullerian tumours are characterized by early extra uterine spread and lymph node metastases. Extra uterine disease and lymph node

metastases are directly related to depth of myometrial invasion and the presence of cervical disease. The presence of heterologous elements does not seem to affect prognosis in terms of the initial extent of disease. New evidence points to a substantial expression of c-kit receptors in MMTs.

ii Endometrial Stromal Tumours and Leiomyosarcomas

Stromal tumours and leiomyosarcoma occur primarily in perimenopausal women between 45 and 50 years of age and there is no relationship to parity (Lurain, 2002). Just like other uterine sarcomas, they have a higher incidence and poorer prognosis in African women. Lower abdominal pain is the commonest presenting symptom especially in leiomyosarcoma and poorer prognosis in black African women than in white women. The histopathologic diagnosis of Leiomyosarcomas (LMS) can be unclear until the time of definitive surgery. Diagnosis of LMS is believed to depend on the number of mitoses (or mitotic count) and the degree of cellular atypia. The diagnosis of LMS versus leiomyoma and leiomyoma with high mitotic activity or uncertain malignant potential is based on the metastatic potential of the tumour. The mitotic count and cellular atypia correlates to this metastatic potential. Although controversy continues to exist regarding the diagnosis of LMS, several studies support the theory that if the mitotic count is less than 5 per 10 high-powered fields (HPF), the tumour is a leiomyoma with negligible metastatic potential regardless of the presence of any cellular atypia. Likewise, the tumour has a high metastatic potential and is considered an LMS, regardless of the degree of cellular atypia, if the mitotic count is

greater than 10 per 10 HPF. Some believe that mitotic count alone is not a good indicator of metastatic potential.

Endometrial Stromal Tumours (EST) can be divided into 2 categories: low-grade EST (LGEST) and high-grade EST (HGEST). Low Grade Endometrial Stromal Tumours (LGEST) is characterized by fewer than 5-10 mitoses per 10 HPF and minimal cellular atypia. These tumours can have a recurrence rate of up to 50% but demonstrate indolent growth and late recurrences. High Grade Endometrial Stromal Tumours (HGEST) have a greater mitotic count and degree of cellular atypia. Risk of recurrence in both LGEST and HGEST is determined not only by histological characteristics but also by surgical stage and extent of disease. Interestingly, some authors believe that true HGEST does not exist.

II. TREATMENT OPTIONS

The first step in the treatment of early uterine sarcoma should be exploratory laparotomy. Total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed in all patients except premenopausal women with leiomyosarcoma (Lurain, 2002). Most studies have found adjuvant post-operative radiation therapy to be of value in decreasing pelvic recurrences and thereby increasing quality of life in patients with localized carcinosarcoma and stromal tumours, but not leiomyosarcomas (Knocke et al, 1998 and Molpus et al, 1998). Adjuvant therapy has been shown to improve the survival for women with stage II – IV disease (Brooks et al, 2004). The literature has revealed that black women have a higher incidence of the most common uterine sarcomas. Brooks et al, (2004) believes

that the poorer survival of black women with uterine sarcoma may be due in part to lower referral for radiation therapy (or other adjuvant therapy) with extension of disease beyond the uterus, given the higher prevalence of stage II disease. It has been shown that when black and white women receive the same adjuvant therapy with disease at the same stage the survival rate is not that different even with other cancer like cervical and breast.

In advanced disease, progestin therapy and doxorubicin-based chemotherapy have a role. Because of the increased tendency for LMS to spread via blood and recur at distant/extra-pelvic sites, whole-pelvic radiotherapy is relatively ineffective. Chemotherapy with doxorubicin, ifosfamide, etoposide, and/or cisplatin may be used of LMS. Recently, gemcitabine and taxotere combination therapy has shown promise in unresectable LMSs of different sites. Patients with MMT limited to the pelvis benefit from whole-pelvic radiation with respect to local control. Those patients with evidence of extra-pelvic disease may respond to additional postoperative therapy with doxorubicin, cisplatin, and/or ifosfamide. These cytotoxic therapies have demonstrated up to a 20% complete response rate in patients with advanced or recurrent disease. Therefore radiation therapy provides local tumour control with no consistent improvement in survival rates. Based on the evidence available chemotherapy and hormonal therapy are better suited for evidence of extra-pelvic spread but yield somewhat inconsistent results. For these reasons, postoperative therapy for uterine sarcomas is quite variable.

Recurrence is very common when dealing with uterine sarcomas. Stage I uterine sarcomas recur in up to 50% of cases. The overall 5 year survival rate for LMS is 15-25%. Stage I LMS has a 58% and 70% 5 year survival after surgery without and with

radiation therapy, respectively. Recurrences commonly occur in the lungs mostly and very rarely localized. Stage I LGEST and HGEST have 5 year survival rates of 80% and 50%, respectively. As expected, advanced disease has a much worse prognosis, with a 5 year survival rate of 0-33% for stages II-IV. Early-stage carcinosarcoma has a 5 year survival rate of approximately 50%, while stages II-IV have a 5-year survival rate of 5-15%. Localized disease, pelvic or extra-pelvic, may be responsive to surgical excision or radiation therapy. Although doxorubicin, ifosfamide, and cisplatin have been studied and used in treatment of distant multi-focal recurrent disease, no definitive choice of chemotherapeutic has been recommended for the treatment of recurrent uterine sarcomas. Evaluation of imatinib mesylate (Gleevec) in advanced and recurrent carcinosarcoma is in progress.

CHAPTER 3:

I. The aims of the study

1. To audit the profile of patients with uterine malignancies (carcinomas and sarcomas) presenting to the gynaecological oncology clinic at IALCH between 2001 and 2006.

2. The aim of the study was to compare uterine malignancies between white women and black women who presented at Inkosi Albert Luthuli Central Hospital Gynaecological Oncology clinic between June 2001 and June 2006.

II. OBJECTIVES

- To compare the type of uterine malignancy and stage at the time of presentation.

- To compare management options taken (surgical vs radiotherapy vs chemotherapy) and the outcome there after.

- To compare any differences in outcome of disease amongst the various ethnic groups presenting to the oncology clinic at IALCH.

III. METHODS

a) The Study design

The study was a retrospective review of clinical records of patients managed at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, KwaZulu Natal, South Africa. Following approval from the institutional post graduate (higher degree committee) and ethics committee, charts of patients treated at the Inkosi Albert Luthuli Central Hospital Gynaecology-Oncology clinic between 01 June 2001 and 30 June 2006 were reviewed. A data collection sheet (Appendix 1) was used to capture data. All information was kept confidential. The data was then submitted to the statistician (Ms Cathy Connolly, MRC Durban) for analysis.

IV. STATISTICAL ANALYSIS

Data was entered using an excel spreadsheet and then exported to Stata 9 (Stata Corp, College Station, TX) for recoding and analysis. Demographic and clinical data are presented for each cancer group. However, the numbers in each cancer group were too small for reliable statistical comparisons so only the frequencies and percentages are presented.

CHAPTER 4

I. RESULTS

There were 118 women with uterine malignancy that presented or were referred to IALCH gynaecological oncology clinic during the study period. Of 118 charts reviewed, data in six charts was incomplete and therefore could not be included in the study. There were 85 patients with endometrial carcinoma (75.9%) and 27 patients with uterine sarcoma (24.1%).

DEMOGRAPHIC PROFILE, CLINICAL DATA AND SPECIAL INVESTIGATIONS (Table 1)

There were far less white patients (9.8%) in the whole study when compared with African patients (47%), who were the majority and Indian women (41%). The majority of patients were African (48%) in the endometrial carcinoma group and Indian in the Uterine Sarcoma group (48%). The majority of women in the endometrial group were greater than the age 60 whereas in the sarcoma group the majority were less than 60 years. Most women fell into the Para 1 to 4 group as compared with the other groups. The commonest presenting symptom was vaginal bleeding in both the endometrial carcinoma and sarcoma groups. The majority of patients {endometrial carcinoma (49%) vs sarcoma (63%)} had hypertension as associated disease and diabetes mellitus was found in 27% of patients in the endometrial group. Only 31% of Pap smears showed malignancy in the endometrial carcinoma group and 25.9% of patients in the whole sarcoma group. Urea and

creatinine were found to be normal in the majority of patients in both sarcoma and endometrial group, so was abdominal ultrasound and chest x-ray in both groups of uterine malignancies.

TREATMENT, STAGING AND COMPLICATIONS OF SURGERY (Table 2)

Surgery was found to be the primary mode of treatment in both endometrial (89%) and uterine sarcoma (82%) groups. Total Abdominal Hysterectomy (TAH) and bilateral salpingo-oophorectomy was the commonest type of surgery for both groups. Lymph node dissection was done in 9% of patients with endometrial carcinoma. Majority of patients who were seen at the combined oncology clinic had surgery performed by the referring hospital where the clinician had not performed surgical staging (lymphadenectomy). A large number of these patients however, were not candidates for surgical staging due to anaesthetic and medical risk factors. The patients who had lymphadenectomy performed were carefully selected according high risk factors for node involvement (policy of the unit). Most patients (53%) in the endometrial group presented with FIGO stage I whereas only 18% of the sarcoma presented in stage I and the majority presented with stage 4 disease. Then 25% of patients with endometrial carcinoma presented with stage 3 which was the second most common stage at the time of presentation for this group. Radiotherapy was the commonest adjuvant therapy for endometrial carcinoma (53%) which is in keeping with the literature. Chemotherapy combined with radiotherapy was rarely used in the endometrial carcinoma group, whereas in the sarcoma group, the majority of patients had chemotherapy (33%) alone. There were 30% of sarcoma patients with local side effects from chemotherapy while most of the endometrial carcinoma group (88%) had

no side effects from the chemotherapy. Eighty percent of endometrial carcinoma patients completed therapy compared to only 52% of uterine sarcoma patients. Nine percent of endometrial carcinoma patients defaulted treatment and only 2 defaulted treatment in the sarcoma group. Nine percent of endometrial carcinoma patients defaulted treatment and only 2 defaulted treatment in the sarcoma group. Ninety five percent of endometrial carcinoma group were still alive on completion of this review and 19% of the uterine sarcoma group died during follow up.

HISTORY, RADIOTHERAPY SIDE EFFECTS AND HIV STATUS (Table 3)

Only 3 patients in the whole study group had recorded use of hormone replacement therapy (HRT) prior to presentation at the clinic. Of the patients who received radiotherapy (53% in the endometrial group and 18% in the sarcoma group), only 2 had side effects (bowel stricture and cystitis) in the sarcoma group and 10 in the endometrial group (6% with GIT side effects and 5% with gynaecological side effects). In the majority of patients (93% in the endometrial group and 92.5% in the sarcoma group) there was no family history of cancer of any origin. However, 5% of patients in the endometrial group had family history of breast carcinoma and 2% had that of endometrial carcinoma. Seven percent of endometrial carcinoma patients were found to be HIV positive and 18.5% of patients with sarcoma were HIV positive. Of the 10 overall HIV positive patients, 3 had stage I disease (endometrial carcinoma), 3 had stage III disease (1 in the sarcoma group and 2 in the endometrial carcinoma group) and 4 had stage IV disease (all being in the sarcoma group). But the number of HIV positive patients was too small to be compared with the HIV negative group.

None of the HIV positive patients were on Anti – retroviral treatment and the average CD4 cell count was 346 μ/cells. Only one HIV positive patient was noted to have died from pneumonia, the rest were still being followed up or receiving treatment for whatever type of cancer that they were diagnosed with. Of note there were no HIV positive patients with uterine malignancy at IALCH until July 2005. EST was excluded from significant testing since there was only 1 patient who presented with this condition during the study period.

CHAPTER 5

I. DISCUSSION

Connell et al. (1999) retrospectively compared the clinicopathologic factors, socioeconomic status, treatments, and outcomes of 70 black and 302 white women treated for surgically staged endometrial carcinoma at their institution. They found black women to have higher-grade tumors, less favourable histological findings, more co-morbid illnesses, and lower socioeconomic indices. On univariate analysis, black women were found to have a worse 5-year disease-free survival than white women (52.8% versus 75.2%; p = 0.001). Other significant factors included stage, grade, lymph node status, extension to the uterine serosa, cervical involvement, histology, adnexal involvement, lymphovascular invasion, myometrial invasion, positive peritoneal cytology, level of education, and household income. After controlling for pathologic and socioeconomic differences in multivariate analysis, race remained a significant prognostic factor (p = 0.008; hazard rate 2.0; (95% confidence interval 1.2 - 3.5). They then concluded that the black race was associated with significantly worse outcomes, even after controlling for clinicopathologic and socioeconomic factors when it came to endometrial carcinoma.

Amant et al (2005) traced 146 patients of which 9 patients were ineligible. Histological subtypes of the remaining 137 patients were - 50 (37%) grade 3 endometrioid carcinoma, 54 (39%) serous or clear cell carcinoma (non-endometrioid carcinoma), and 33 (24%) carcinosarcomas. The distribution of early stage disease (I and II) was 67, 46, and 78% for grade 3 endometrioid, non-endometrioid, and carcinosarcoma, respectively. Although they could not trace differences in hematogenic and transperitoneal spread among the three subtypes, they reported that non-endometrioid and carcinosarcomas were more likely to spread to pelvic and para-aortic lymph nodes (p< 0.01). Using univariate analysis, both stage ($p < 0.006$) and histological type appeared to determine the outcome, whereas lympho-vascular space

infiltration ($p < 0.25$) and age ($p < 0.07$) were not significantly different between the three histological subtypes that were studied. Cox Regression multivariate analysis performed on the 127 women suffering from the three histological subtypes suggested that both stage III–IV disease ($p < 0.00001$) and histological type (carcinosarcoma) ($p < 0.003$) were of prognostic significance. Analyzing cases limited to stage I–II endometrial cancer, 24/28 (86%) grade 3 endometrioid, 18/24 (75%) non-endometrioid, and 11/25 (44%) carcinosarcomas survived, suggesting a worse outcome for endometrial carcinosarcoma when compared to the other subtypes ($p < 0.008$). A higher incidence of pulmonary metastases explained the worse outcome for early stage carcinosarcoma ($p < 0.006$), whereas the incidence of liver metastasis, transperitoneal spread, or recurrences in lymph nodes or vagina were comparable between the three pathologic subtypes. They then concluded that although endometrial carcinosarcoma originates from epithelial cancer, the intrinsic more aggressive tumour biology suggests that this subtype should not be incorporated in studies on high-risk epithelial endometrial cancer.

Aziz et al (1993) reviewed 290 patients between 1975 and 1990 who presented at the Health Science Centre at Brooklyn and Kings County Hospital Centre of which 47.2% were black and 46.9% were white. They found that of the patients who presented in stage III disease, 88.89% were black and 11.1% were white ($p = 0.034$). They also reported that with grade III disease, 70.5% were black and 29.5% were white ($p = 0.008$). Seventy two percent of patients with positive lymph nodes were in black patients compared to the 28% in white patients ($p = 0.01$). Their overall ten-year corrected survival for white and black patients was 72% and 40%, respectively ($p = 0.0003$).

In our study the number of white women was too small to be compared with black women (n = 10 vs 51) but even so, African women and Indian were associated with worse disease and outcome (only 1 White patient presented with advanced disease – EST). There were 41.2% of African women with early stage disease (Stage I) compared with 50% of the Indian women. Over 82% of all patients were treated with surgery as the primary mode of treatment (African = 88.2%, Indian = 84% and white = 82%). Of the 12.9% serous papillary adenocarcinoma subtype, 54% were Indian and 36% were African and 1 patient was Coloured. Three coma five percent of Indian patients had serous subtype of endometrial carcinoma. Currently there is no literature comparing Indian women with endometrial cancer to black women with endometrial cancer but looking at our results one wonders whether disease progression is worse in the South African Indian community when compared to the African women.

Randall and Armstrong (2003) analyzed 1992 to 1998 Surveillance, Epidemiology, and End Results data for 21,561 women with epithelial cancers of the endometrium. They found unadjusted hazard ratio (HR) for death from endometrial cancer for African-American women compared with white women to be 2.57. However, African-American women were significantly more likely to present with advanced-stage disease and have poorly differentiated tumours or tumours with an unfavourable histological type and were significantly less likely to undergo definitive surgery at all stages of disease. After adjusting for tumour and socio-demographic characteristics lowered the HR for African-American women to 1.80. Further adjustment for the use of surgery reduced the HR to 1.51. They found that the association between surgery and survival was stronger among white women (HR 0.26) than among African-American women (HR 0.44). They then concluded that African-American women with endometrial cancer are significantly less likely to undergo primary surgery and

have significantly shorter survival than white women with endometrial cancer. Racial differences in treatment are associated with racial differences in survival. The association between use of surgery and survival is weaker among African-American than white women, raising questions about potential racial differences in the effectiveness of surgery.

Even though we could not compare white women with African women there were many patients with endometriod subtype (82.4%) and over 88% of African patients had surgery as primary mode of treatment and only 4 patients were recorded to have demised. White women could not be compared to African women because of the small number of white patients, but there was no major difference in disease progression, response to treatment and stage of presentation when African women were compared to the Indian women.

Brooks et al. (2004) used cases from Surveillance, Epidemiology, and End Results (SEER) program to compare uterine sarcoma among women >35 years of age. Using data from 1989 to 1999, they compared race-specific age-adjusted incidences, histological distributions, extent of disease at diagnosis, and race-specific survival. During the period of 1989–1999, 2677 women were diagnosed with uterine sarcoma, 2098 (78%) of whom were white and 420 (16%) of whom were black, and 159 (6%) of whom were of other races. In their study the overall age-adjusted incidence for blacks was twice that of whites and more than twice that of women of other races ($p <$ 0.0001). Racial differences in the incidence of uterine sarcoma existed for leiomyosarcoma with blacks being affected more than other race groups ($p < 0.01$) and carcinosarcoma presenting the same picture ($p < 0.001$), but not for other histological types. Blacks with stage II disease were less likely to receive radiation in

addition to surgery compared to whites (33% vs. 54%, $p < 0.05$). Five year relative survival of patients with disease beyond the uterus was significantly longer for those who received radiation and surgery compared to those that received surgery alone. They then concluded that adjuvant therapy improved survival for women with stage II–IV disease and survival of black and white patients who received comparable treatment was similar.

In our study there were 27 patients with uterine sarcoma so it was not possible to compare the different race groups. There were 8 Indian women with carcinosarcoma and 6 African women; 5 Indian women with leiosarcoma and 6 African women with only 1 white patient in this group. Seventy one percent of carcinosarcoma patients had surgery compared with 92% of patients with leiomyosarcoma even though only 25% (Carcinosarcoma) and 14% (Leiomyosarcoma) presented in stage I. Twenty one percent of Carcinosarcoma patients demised and 17% of the leiomyosarcoma group.

II. CONCLUSION

Connell et al. (1999) retrospectively compared the clinicopathologic factors, socioeconomic status, treatments, and outcomes of 70 black and 302 white women who were treated for surgically staged endometrial carcinoma at their institution.

Black women had higher-grade tumours, less favourable histological findings, more co-morbid illnesses, and lower socioeconomic indices. Randall and Armstrong (2003) analyzed 1992 to 1998 Surveillance, Epidemiology, and End Results data for 21,561 women with epithelial cancers of the endometrium. They found unadjusted hazard ratio (HR) for death from endometrial cancer for African-American women compared with white women to be 2.57. However, African-American women were significantly more likely to present with advanced-stage disease and have poorly differentiated tumours or tumours with an unfavourable histological type and were significantly less likely to undergo definitive surgery at all stages of disease.

The majority of patients seen at IALCH are African or Indian reflecting the demographics of the province. White patients seek medical assistance in the private sector due to better financial circumstances. Therefore comparison between African and white patients was not possible but assessment of disease and disease behaviour in African and Indian patients was done and it was realised that when they present early and appropriate management applied, the outcome is not that different from that described for white patients in other studies. There is a need for a bigger and better review comparing white women to African women in South Africa so that we can compare it with what is reported in other countries.

APPENDIX 1

DATA COLLECTION SHEET FOR PATIENTS WITH UTERINE TUMOURS								
RACE								
		1- WH		2 - AF		3- IN		

AGE		
	1- (<40YRS)	2- (41-60YRS)
		3- (61-80YRS)
PARITY		
	1- (<1)	2- (1-4)
		3- (>4)
PRESENTING SYMPTOMS		
	1- BLE	2- PVD
		3- PLM
MEDICAL CONDITIONS		
	1- DM	2- HPT
		3- OTH
		4 - NIL
CLINICAL FEATURES		
	BP 1-NOR	ABD MASS 1-<12W
	2-HPT	2- >13W
		LMP 1-ING
		2-GEN
		3-NIL
INVESTIGATIONS		
	PAP 1-NEG	HB 1-LOW
	2-LGSIL	2-NOR
	3-HGSIL	
	4-CAN	HISTO 1- ENDO
HIST SUBGROUP		2- LEIO
1-ENDO		3-MMMT
2-SER		4- EST
3-MUCI		
4-SERPAP	CREATININE	CXR 1- NOR
5-CLEAR	1- NOR	2- PLE
	2- ABN	3- ATE
		4- MET
		U/S ABD 1- NOR
		2- LIV
		3- HYD
		4- ASC
PRIMARY MODE OF TREATMENT		
	1- SUR	2- XRT
		3- SYM
TYPES OF SURGERY		
	1- TAH/BSO	2- VH
		3- LVH
	5- OMT	6- APE
		7- TAH/LND/BSO
FIGO STAGING		

	1A- 1		1B- 2		1C- 3		
		IIA- 4		IIB- 5			
		IIIA- 6		IIIB- 7		IIIC- 8	
		IVA- 9		IVB- 10		11 - NONE	
ADJUVANT THERAPY							
		1- SUR		2- XRT		3- CHE	
		5- HOR		6- OTH		7- NIL	
COMPLICATIONS OF SX							
		1- YES		2- NO			
SIDE EFFECTS OF CHEMO							
		haem - 1	GIT - 2	local - 3	renal - 4		5- NIL
COMPLETION OF THERAPY							
		1- YES		2- NO			
FOLLOW UP							
		DEF- 1	<1YR- 2	1-4YRS- 3		>4YRS- 4	
CLINICAL OUTCOME POST RX							
		1- ALIVE		2- DEMISED			
FAMILY HISTORY							
		1-CA BRE		2- CA END		3- CA BOW	
			5- CA OVA				
HRT		1- YES			2- NO		
S/E OF XRT		GIT – 1		2- NO		GYN - 3	
HIV STATUS		POS – 1		NEG - 2		UNK - 3	

Key:

Race:

WH – White

AF – African

IN – Indian

CO - Coloured

Presenting symptoms:

BLE – Bleeding

PVD – Per vaginal discharge

PLM – Pelvic mass

OTH - Other

Medical Conditions:

DM – Diabetes Mellitus

HPT– Hypertension

Clinical features:

BP - Blood pressure

NOR – Normal

HPT – Hypertension

ABD – Abdominal

LMP – Lympadenopathy

ING – Inguinal

GEN- Generalized

ASC - Ascites

Investigations:

NEG – negative

LGSIL – low grade squamous intraepithelial lesion.

HGSIL – High grade squamous intraepithelial lesion.

CAN – Cancer

Hb – haemoglobin

NOR – normal

ABN – abnormal

Histo Subgroup:

ENDO –

Types of Surgery:

TAH – Total

Adjuvant Therapy:

SUR – Surgery

Ultrasound Abdomen:

NOR – normal

HISTO – Histology

ENDO –

Endometrioid – Endometrial

SER – Serous

MUCI – Mucinous

SERPAP – Serous Papillary

abdominal hysterectomy

VH – Vaginal Hysterectomy

LVH – Laparoscopy assisted vaginal hysterectomy

RADH – Radical Hysterectomy

LND – lymph node dissection

OMT – Omentectomy

APE – Appendixectomy

BSO – Bilateral Salpingo-oophorectomy

XRT – Radiotherapy

HOR – Hormonal

CHE – Chemotherapy

CRT – Chemoradiotherapy

LIV – liver metastasis

HYD – hydronephrosis

LEIO – Leiomyosarcoma

MMMT – Mixed Mullerian Tumour

EST – Endometrial Sarcoma Tumor

APPENDIX 2

Table 1:

DEMOGRAPHIC PROFILE OF PATIENTS, CLINICAL DATA AND SPECIAL INVESTIGATIONS

			Sarcomas		
	Endometrial		**Leio**	**CS**	**EST**

	(n = 85)		(n = 12)		(n= 14)		(n = 1)	
	n	%	n	%	N	%	N	%
Race								
White	10	12%	1	8%	0	0%	0	0%
African	41	48%	6	50%	6	43%	0	0%
Indian	32	38%	5	42%	8	57%	1	100%
Coloured	2	2%	0	0%	0	0%	0	0%
Age								
< = 60 yrs	34	40%	9	75%	4	29%	0	0%
> 60 yrs	51	60%	3	25%	10	71%	1	100%
Parity								
< 1	10	12%	3	25%	2	14%	1	100%
1 to 4	45	53%	9	75%	4	29%	0	0%
> 4	30	35%	0	0%	8	57%	0	0%
Presenting symptoms								
BLE	80	94%	11	92%	13	93%	1	100%
PVD	8	9%	1	8%	2	14%	0	0%
PLM	0	0%	1	8%	0	0%	0	0%
Other	0	0%	0	0%	0	0%	0	0%
Medical Condition								
DM	23	27%	0	0%	4	29%	0	0%
HPT	42	49%	6	50%	10	71%	1	100%
Other	1	1%	0	0%	1	7%	0	0%
Nil	32	38%	6	50%	2	14%	0	0%
INVESTIGATIONS								
Pap smear								
Neg	55	65%	9	75%	9	64%	1	100%
LGSIL	2	2%	1	8%	0	0%	0	0%
HGSIL	2	2%	0	0%	0	0%	0	0%
CAN	26	31%	2	17%	5	36%	0	0%
Blood Pressure								
Low	53	62%	9	75%	7	50%	0	0%
Normal	32	38%	3	25%	7	50%	1	100%
Urea								
Normal	67	79%	9	75%	11	79%		0%
Abnormal	18	21%	3	25%	3	21%		0%
Creatinine								
Normal	76	89%	11	92%	10	71%	1	100%
Abnormal	9	11%	1	8%	4	29%	0	0%
Chest xray								
Normal	79	93%	8	67%	10	71%	0	0%
PLE	3	4%	0	0%	1	7%	0	0%
ATE	3	4%	4	33%	3	21%	0	0%
ATE/MET	0	0%	0	0%	0	0%	1	100%
U/S ABD								
Normal	75	88%	8	67%	8	57%	0	0%

LIV	2	2%	2	17%	2	14%	0	0%
HYD	1	1%	0	0%	0	0%	0	0%
ASC	6	7%	0	0%	4	29%	0	0%
LIV/ASC	1	1%	2	17%	0	0%	1	100%
*EST excluded from significance testing								

Key

a. Presenting symptoms	**b. Medical condition**
BLE – bleeding PVD – vaginal discharge PLM – pelvic mass	DM – diabetes mellitus HPT – hypertension
c. Pap smear	**d. Chest xray**
Neg – negative LGSIL – low grade squamous intraepithelial lesion HGSIL – high grade squamous intraepithelial lesion CAN – cancer	PLE – pleural effusion ATE – atelactasis MET - metastasis
e. Ultrasound abdomen	**f. Sarcomas**
LIV – liver metastasis HYD – hydronephrosis ASC - Ascites	Leio – Leiomyosarcoma CS – Carcinosarcoma EST – Endometrial Sarcoma Tumours

Table 2:

TREATMENT, STAGING AND COMPLICATIONS OF SURGERY

			Sarcomas					
	Endometrial		Leio		CS		EST	
	(n = 85)		(n = 12)		(n= 14)		(n = 1)	
	n	%	n	%	N	%	N	%
Primary Mode of RX								
Surgery	76	89%	11	92%	10	71%	1	100%
XRT	7	8%	0	0%	2	14%	0	0%
SYM	2	2%	1	8%	2	14%	0	0%
Types of Surgery								
TAH/BSO	63	83%	7	58%	10	71%	1	100%
VH	4	5%	1	8.3%	0	0%	0	0%
RADHY	1	1%	0	0	0	0%	0	0%
TAH/LND/B	7	9%	1	8.3%	0	0%	0	0%
TAH/BSO/OMT/APE	1	1%	0	0	0	0%	0	0%
NIL	9	12%	3	25%	4	29%	0	0%
FIGO STAGING								
1	45	53%	3	25%	2	14%	0	0%
2	12	14%	1	8%	4	29%	0	0%
3	21	25%	2	17%	3	21%	0	0%
4	2	2%	6	50%	3	21%	1	100%
no stage	5	6%	0	0%	2	14%	0	0%
Adjuvant therapy								
XRT	45	53%	4	33%	1	7%	0	0%
CHE	5	6%	3	25%	6	43%	0	0%
XRT&CHE	9	11%	3	25%	5	36%	0	0%
Nil	26	31%	2	17%	2	14%	1	100%
Complications of Surgery								
Yes	14	16%	2	17%	2	14%	0	0%
No	71	84%	10	83%	12	86%	1	100%
Side effects of Chemo								
Haem	3	4%	0	0%	0	0%	0	0%
GIT	2	2%	0	0%	1	7%	0	0%
Local	3	4%	3	25%	5	36%	0	0%
Renal	2	2%	1	8%	1	7%	0	0%
Nil	75	88%	8	67%	7	50%	1	100%
Completion of therapy								
Yes	68	80%	6	50%	8	57%	0	0%
No	17	20%	6	50%	6	43%	1	100%
Follow up								
Default	8	9%	0	0%	2	14%	0	0%
< 1yr	30	35%	4	33%	4	29%	1	100%
1-4yrs	46	54%	6	50%	7	50%	0	0%
> 4 yrs	1	1%	2	17%	1	7%	0	0%
Clinical Outcome								

Alive	81	95%	10	83%	11	79%	1	100%
Demised	4	5%	2	17%	3	21%	0	0%
*EST excluded from significance testing								

Key

a. **Primary mode of treatment**	b. **Types of surgery**
XRT – radiotherapy SYM – symptomatic	TAH – Total Abdominal Hysterectomy BSO – Bilateral Salpingo-oophorectomy VH – Vaginal hysterectomy RADHY – Radical hysterectomy LND/B – Lymph node dissection/biopsy OMT – omentectomy APE – Appendecectomy
c. Adjuvant therapy	**d. Side effects chemotherapy**
XRT – radiotherapy CHE – Chemotherapy XRT & CHE – radiotherapy and chemotherapy	Haem – haematological GIT – gastro-intestinal

Table 3:

HISTORY, RADIOTHERAPY SIDE EFFECTS AND HIV STATUS

			Sarcomas					
	Endometrial		**Leio**		**CS**		**EST**	
	(n = 85)		**(n = 12)**		**(n= 14)**		**(n = 1)**	
	n	**%**	**n**	**%**	**N**	**%**	**n**	**%**
Family History								
CA BRE	4	5%	1	8%	0	0%	0	0%
CA END	2	2%	0	0%	1	7%	0	0%

Nil	79	93%	11	92%	13	93%	1	100%
HRT								
Yes	2	2%	1	8%	0	0%	0	0%
No	83	98%	11	92%	14	100%	1	100%
S/E of XRT								
GIT	5	6%	0	0%	1	7%	1	100%
No	76	89%	12	100%	13	93%	0	0%
GYN	4	5%	0	0%	0	0%	0	0%
HIV Status								
Pos	6	7%	4	33%	1	7%	0	0%
Neg	64	75%	7	58%	8	57%	1	100%
Unk	15	18%	1	8%	5	36%	0	0%
*EST excluded from significance testing								

Key

a. **Family history**	c. **Side effects of radiotherapy**
CA BRE – carcinoma of the breast CA END – carcinoma of the endometrium	GIT – gastro-intestinal GYN – gynaecological No – none
b. **HIV Status**	
Pos – positive Neg – negative Unk – unknown	

REFERENCE

Aapro M, Bolis G, Chevallier B et al. An EORTC-GCCG randomized phase II trial of doxorubicin (dox) versus dox-cisplatin (CDDP) in endometrial carcinoma. *Proc Am Soc Clin Oncol* 1994; 13: 275.

Abeler VM and Kjorstad KE. Clear cell carcinoma of the endometrium: histopathologic and clinical study of 97 cases. *Gynecol Oncol* 1991; 40: 207-217

Amant F, Vloeberghs V, Woestenborghs H et al. Transition of epithelial towards mesenchymal differentiation during ovarian carcinosarcoma tumorigenesis, *Gynecol Oncol* 2003; 90: 372–377.

Amant F, Cadron I, Fuso L, et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. *Gynecol Oncol* 2005; 98(2): 270 – 80.

Amant F, Moerman P, Neven P, et al. Endometrial Cancer. *The Lancet* 2005; 366, 491 – 505.

Austin H, Austin JM Jr, Partridge EE et al. Endometrial cancer, obesity, and body fat distribution. *Cancer Res* 1991, 51: 568-572.

Ayoub J, Audet-Lapointe P, Methot Y et al. Efficacy of sequential cyclical hormonal therapy in endometrial cancer and its correlation with steroid hormone receptor status. *Gynecol Oncol* 1988; 31: 327-337.

Aziz H, Rotman M, Hussain F, et al. Poor survival of black patients in carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys* 1993; 27: 293 – 301.

Bandera EV, Kushi LH, Olson SH, et al. Alcohol consumption and endometrial cancer: some unresolved issues, *Nutr Cancer* 2003; 45: 24–29.

Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983; 15: 10–17.

Boike G, Lurain J and Burke J. A comparison of laparoscopic management of endometrial cancer with traditional laparotomy. *Gynecol Oncol* 1994; 52: 105.

Bourne TH, Campbell S, Steer LV, et al. Detection of endometrial by trans- vaginal ultrasound with color flow imaging and blood flow analysis: a preliminary report. *Gynecol Oncol* 1991; 40: 253-259.

Brinton LA, Berman ML, Mortel R et al. Reproductive, menstrual, and medical risk factors forendometrial cancer: results from a case-control study. *Am J Obstet Gynecol* 1992; 167: 1317-1325.

Brooks SE, Zhan M, Cote T, et al. Surveillance, epidemiology, and results analysis of 2677 cases of uterine sarcoma 1989-1999. *Gynecol Oncol* 2004; 93: 204-8.

Burke TW, Gershenson DM, Morris M, et al. Postoperative adjuvant cisplatin, doxorubicin, and cyclophosphomide (PAC) chemotherapy in women with high risk endometrial carcinoma. *Gynecol Oncol* 1994; 55: 47

Carcangiu ML and Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. *Gynecol Oncol* 1992; 47: 298-305.

Cauley JA, Gutai JP, Kuller LH et al. The epidemiology of serum sex hormones in postmenopausal women. *Am J Epidemiol* 1989; 129: 1120-1131.

Chambers JT and Chambers SK. Endometrial sampling: When? Where? Why? With what? *Clin Obstet Gynecol* 1992; 35: 28-39.

Chan JK, Lin YG and Monk BJ. Vaginal hysterectomy as primary treatment of endometrial cancer in medically compromised women. *Obstet Gynecol* 2001; 97: 707-711.

Chubak J, Tworoger SS, Yasui Y, et al. Associations between reproductive and menstrual factors and postmenopausal sex hormone concentrations, *Cancer Epidemiol Biom Prev* 2004; 13:1296–1301.

Clark TJ, Mann CH and Shah N et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. *Brit J Obstet Gynaecol* 2002; 109: 313–321.

Cohen CJ, Bruckner HW, Deppe G et al. Multidrug treatment of advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Obstet Gynecol* 1984; 63: 719-726.

Connell PP, Rotmensch J and Wagger SE. Race and clinical Outcome in Endometrial carcinoma. *Obstet Gynaecol* 1999; 94: 713-720.

Cragun JM, HavrileskyLJ and Calingaert B et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer, *J Clin Oncol* 2005; 23: 3668–3675.

Crawford SC, De Caestecker L, Gillis CR et al. Staging quality is related to the survival of women with endometrial cancer: a Scottish population based study, *Brit J Cancer* 2002; 86: 1837–1842.

Creasman WT, Morrow CP, Bundy BN et al. Surgical pathologic spread patterns of endometrial cancer, *Cancer.* 1987; 60: 2035–2041.

Creutzberg CL, van Pattern WLJ and Koper PCM. Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicenter randomized trial. *The Lancet*, 2000; 355: 1404-1411

Davidson BJ, Gambone JC, Lagasse LD et al. Free estradiol in postmenopausal women with and without endometrial cancer. *J Clin Endocrin Met* 1981; 52: 404-408.

Dijkhuizen FPHLJ, Mol BWJ, Brolmann HAM et al. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a metaanalysis. *Cancer* 2000; 89: 1765-1772

Dubeshter B, Warshal DP, Angel C, et al. Endometrial carcinoma: the relevance of cervical cytology. *Obstet Gynecol* 1991; 77: 458-462

Du Toit GC. Malignancies of the Uterine Corpus, in: *Clinical Gynaecology (second edition),* Odendaal HJ, Schaetzing AE, and Kruger TF, South Africa, JUTA, 2001, 511 – 516.

Elwood JM, Cole P, Rothman KJ et al. Epidemiology of endometrial cancer. *Brit J Hosp Med* 1997; 59: 1055-1060.

Enriori CL and Reforzo Membrives J. Peripheral aromatization as a risk factor for breast and endometrial cancer in postmenopausal women: a review. *Gynecol Oncol* 1984; 17: 1-21.

Evans DGR. Genetics of gynaecological cancer. *Curr Obstet Gynecol* 1995; 5: 201 - 205.

Farhi DC, Nosanchuk J and Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. *Obstet and Gynecol*; 1986, 68: 741-745.

Fleming GF, Brunetto VL, Bentley R et al. Randomized trial of doxorubicin (dox) plus cisplatin (cis) versus dox paclitaxel (tax) plus granulocyte colony-stimulating factor (G-CSF) in patients with advanced or recurrent endometrial cancer: a report on Gynecologic Oncology Group (GOG) protocol 163. *Proc Am Soc Clin Oncol* 2000; 19: 270.

Franchi M, Ghezzi F, Melpignano M et al. Clinical value of intraoperative gross examination in endometrial cancer, *Gynecol Oncol* 2000; 76: 357–361.

Gemignani M, Curtin JP, Zelmanovich J, et al. Laparoscopic-assisted vaginal hysterectomy for endometrial cancer: clinical outcomes and hospital charges. *Gynecol Oncol,* 1999; 73: 5-11.

Gimpleson RJ and Rappold HO. A comparative study between panoramic hysteroscopy with directed biopsies and dilation and curettage: a review of 276 cases. *Am J Obstet and Gynecol* 1988; 158: 489-492.

Goff BA, Kato D, Schimdt RA et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol* 1994; 54: 264-268

Goodman MT, Wilkens LR, Hankin JH et al. Association of soy and fiber consumption with the risk of endometrial cancer. *Am J Epidemiol* 1997; 146: 294-306.

Gordon MD and Ireland K. Pathology of hyperplasia and carcinoma of the endometrium. *Sem Oncol* 1994; 21: 64-70.

Harlow BL, Weiss NS and Lofton S. The epidemiology of sarcomas of the uterus. *J Nat Cancer Inst* 1986; 76: 399-402.

Henderson BE, Casagrande JT, Pike MC et al. The epidemiology of endometrial cancer in young women. *Brit J Cancer* 1983; 47: 749-756.

Hendrickson M, Ross J, Eifel P et al. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. *Am J Surg Path* 1982; 6: 93-108.

Hill HA, Coates RJ, Austin H, et al. Racial differences in tumour grade among women with endometrial cancer. *Gynecol Oncol* 1995; 56(2): 154-63.

Hinkula M, Pukkala E, Kyyronen P et al. Grand multiparity and incidence of endometrial cancer: a population-based study in Finland, *Int J Cancer* 2002; 98: 912–915.

Holub Z, Jabor A, Bartos P, et al. Laparoscopic surgery for endometrial cancer: long term results of multicenter study. *Euro J Gynecol Oncol* 2002; 23: 305-310.

Hubacher D and Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review, *Obstet Gynecol Surv* 2002; 57:120–128.

International Federation of Gynaecology and Obstetrics (FIGO). Annual report on the results of treatment in gynaecologic cancer. *Int J Obstet Gynecol* 1989; 28: 189-193.

Jung RT. Obesity as a disease. *Brit Med Bul* 1997; 53: 307-321.

Kauppila A. Estrogen and Progestin receptors as prognostic indicators in Endometrial cancer: A review of literature. *Acta Oncol*, 1989; 28: 561.

Kelly RM and Baker WH. Progestational agents in the treatment of carcinoma of the endometrium. *New Eng J Med*, 1961; 264: 216-222.

Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol* 1995; 56: 29-33

Knocke TH, Kucera H, Dotfler D et al. Results of postoperative radiotherapy in the treatment of sarcoma of the corpus uteri. *Cancer,* 1998; 83: 1972-1979.

Kucera H, Vavra N and Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. *Gynecol Oncol* 1990; 38: 99-104.

Kupelian PA, Eifel PJ, Tornos C, et al. Treatment of endometrial carcinoma with radiation therapy alone. *Int J Rad Oncol Biol Phy* 1993; 27: 817-824

Kurman RJ, Kaminski PF, and Norris HJ. The behaviour of endometrial hyperplasia: a long term study of untreated hyperplasia in 170 patients. *Cancer* 1985; 56: 403-412.

Kurman RJ and Scully RE. Clear cell carcinoma of the endometrium: an analysis of 21 cases. *Cancer* 1976; 37: 872-882.

Landis SH, Murray T, Bolden S et al. Cancer statistics. *Cancer* 1999; 49: 8-31.

Lawton F. How can we improve the prognosis of endometrial cancer? *Prog Obstet Gynecol* 2003; 16: 343-355

Lehoczky O, Busze P, Ungar L. Advanced stage endometrial carcinoma: treatment of nonoperable patients with intracavitary radiation therapy alone. *Gynecol Oncol* 1991; 43: 211-216.

Levi F, La Vecchia C, Negri E et al. Selected physical activities and the risk of endometrial cancer. *Brit J Cancer* 1993, 67: 846-851.

Liu JR, Conaway M, Rodriguez GC et al. Relationship between race and interval to treatment in endometrial cancer. *Obstet Gynecol* 1995; 86: 486-90.

Lurain JR.Uterine Cancer, in: *Novak's Gynaecology, 13th edition*, Berek JS, Philadelphia, LIPPINCOTT WILLIAMS & WILKINS, 2002, 1143 – 1198.

Mariani A, Webb MJ and Keeney GL. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. *Gynecol Oncol* 2001; 83: 158-163.

McPherson CP, Sellers TA, Potter JD et al. Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. *Am J Epidemiol* 1996; 143: 1195-1202.

Melhern MF and Tobon H. Mucinous adenocarcinoma of the endometrium: a clinico-pathologic review of 18 cases. *Int J Gynecol Path* 1987; 6: 347-355.

Molpus KL, Redlin-Frazier S, Reed G, et al. Postoperative pelvic irradiation in early stage uterine mixed mullerian tumours. *Euro J Gynecol Oncol* 1998; 19: 541-546.

Morrow CP, Bundy B, Homesely H, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high risk endometrial carcinoma, stage I and occult stage II. *Gynecol Oncol* 1990; 36: 166-171.

Parazzini F, La Vecchia C, Moroni S et al. Family history and the risk of endometrial cancer. *Int J Cancer* 1994; 59: 460-462.

Parslov M, Lidegaard O, Klintorp S et al. Risk factors among young women with endometrial cancer: a Danish case-control study. *Am J Obstet Gynecol* 2000; 182: 23-29.

Platz C and Benda J. Female genital tract cancer. *Cancer* 1995; 75: 270–294.

Price FV, Chambers SK, Carcanghn KE, et al. Intravenous Cisplatin, Doxorubicin and Cyclophosphomide in the treatment of Uterine Papillary Serous Carcinoma (UPSC). *Gynecol Oncol* 1993; 51: 583-589.

Quin MA and Campbell JJ. Tamoxifen therapy in Advanced or recurrent Endometrial cancer. *Gynecol Oncol* 1989; 32 (1): 1-3.

Randall TC and Armstrong K. Differences in treatment and outcome between African-American and White women with Endometrial cancer. *J clin Oncol* 2003; 21: 4200 – 4206.

Resnik E and Taxy JB. Neoadjuvant chemotherapy in uterine papillary serous carcinoma. *Gynecol Oncol* 1996; 62: 123-127.

Ronnett B, Zairo R, Ellenson L, et al. Endometrial cancer: *In Blausteins Pathology of the female genital tract , 5th Edition* 2002: 501 – 560.

Schiller W. Mesonephroma ovarii. *Am J Cancer* 1939; 35: 1-21.

Schneider V. Vaginal cuff recurrence of endometrial cancer treated by laparoscopic assisted vaginal hysterectomy, *Gynecol Oncol* 2004; 94: 861–863.

Schottenfeld D. Epidemiology of endometrial neoplasia. *J Cell Biol Sup* 1995; 23: 151-9.

Sherphard JH. FIGO annual report on the results of treatment in gynaecologic cancer. *Int J Gynecol Obstet* 1989;28:189-90.

Sherman ME, Bitterman P, Rosenshein NB, et al. Uterine serous carcinoma. *Am J Surg Path* 1992; 16: 600-610

Sherman ME and Devesa SS. Analysis of racial differences in incidence, survival and mortality for malignant tumours of the uterine corpus. *Cancer* 2003; 98: 176-86.

Sonoda Y, Zerbe M, Smith A, et al. High incidence of positive peritoneal cytology in low risk endometrial cancer treated by laparoscopically assisted vaginal hysterectomy. *Gynecol Oncol* 2001; 80: 378–382.

Stockwell HG and Lyman GH. Cigarette smoking and the risk of female reproductive cancer. *Am J Obstet Gynecol* 1987; 157: 35-40.

Suvanto-Luukkonen E, Sundstrom H, Penttinen J et al. Insulin-like growth factor-binding protein-1: a biochemical marker of endometrial response to progestin during hormone replacement therapy. *Maturitas* 1995; 22: 255–262.

Swanson CA, Potischman N, Wilbanks GD et al. Relation of endometrial cancer risk to past andcontemporary body size and body fat distribution. *Cancer Epidemiol Biom Prev* 1993; 2: 321-327.

Sutton GP, Brill L, Michael H, et al. Malignant papillary lesions of the endometrium. *Gynecol Oncol* 1987; 27: 294-304.

Tobon H, and Watkins GJ. Secretory adenocarcinoma of the endometrium. *Int J Gynecol Path* 1985; 4: 328-335.

Unfer V, Casini ML, Costabile L, et al. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. *Fert Steril* 2004; 82: 145–148.

Xu WH, Zheng W, Xiang YB et al. Soya food intake and risk of endometrial cancer among Chinese women in Shanghai: population based case-control study, *Brit Med J* 2004; 328: 1285.

Yu CK, Cutner A, Mould T et al. Total laparoscopic hysterectomy as a primary surgical treatment for endometrial cancer in morbidly obese women. *Brit J Obstet Gynecol* 2005; 112: 115–117.

Weiderpass E, Adami HO, Baron JA et al. Risk of endometrial cancer following oestrogen replacement with and without progestins. *J Nat Cancer Inst* 1999; 91: 1131-1137.

Weiderpass E, Adami HO, Baron JA et al. Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Caus Cont* 1999; 10: 277-284.

Winter III WE and Gosewehr JA. Uterine Cancer @ eMedicine.com 2006.

Zaino RJ, Kurman R, Herbold D et al. The significance of squamous differentiation in endometrial carcinoma. *Cancer* 1991; 68: 2293-2302.

Zaino RJ, Kurman RJ, Diana KL et al. The utility of the revised International Federation of Gynaecology and Obstetrics histologic grading of endometrial adenocarcinoma using a defined nuclear grading system. *Cancer* 1995; 75: 81–86.

Zanotti KM, Belinson JL, Kennedy AWet al. The use of paclitaxel and platinum-based chemotherapy in uterine papillary serous carcinoma. *Gynecol Oncol* 1999; 74: 272-277

Zucker PK, Kasdon EJ and Feldstein ML. The validity of Pap smear parameters as predictors of endometrial pathology in menopausal women. *Cancer* 1985; 56: 2256-2263.