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Retrospective record review of patients diagnosed with endometrial cancer and carcinosarcoma at Rahima Moosa mother and child hospital receiving treatment at Charlotte Maxeke Johannesburg academic hospital

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RETROSPECTIVE RECORD REVIEW OF PATIENTS DIAGNOSED WITH ENDOMETRIAL CANCER AND CARCINOSARCOMA AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL RECEIVING TREATMENT AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology.

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DECLARATION

I, Susan Jennifer Branch, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

SJ Branch

25th day of January2016

ABSTRACT

Introduction

Endometrial cancer is the most common Gynaecological cancer in developed countries, however, in South Africa it is ranked only the eighth highest. Previous research has shown that black women are diagnosed at a younger age, have a higher incidence of type II endometrial cancer and uterine carcinosarcoma and have a worse overall survival than white women. Government hospitals are busy with large numbers of patients seen daily resulting in longer waiting times for patients requiring surgery and adjuvant treatment for cancer.

Patients and Methods

This was a retrospective cross sectional descriptive study of patients diagnosed with endometrial carcinoma and uterine carcinosarcoma at Rahima Moosa Mother and Child Hospital (RMMCH) between 2009 and 2013. Patient files from both RMMCH and Charlotte Maxeke Johannesburg Hospital (CMJAH) were reviewed. Patients were initially seen at RMMCH, some underwent surgery and they were then referred to CMJAH for adjuvant treatment. Files from both hospitals were reviewed. 55 files were obtained at RMMCH and 50 patients were referred to CMJAH for further treatment.

Results

The most common histological types of endometrial cancer were low grade adenocarcinoma (34.54%) and uterine carcinosarcoma (25.45%). 56.36% of patients presented with early disease (stage 1/2) and 43.64% with advanced disease (stage 3/4). The overall disease free survival was 75.67% at one year, with 8.10% of patients with metastases and 16.21% of patients having died within one year. 53.70% of patients waited less than 62 days until definitive management with 14.81% who waited for more than six months for surgery.

Conclusion

We found a high frequency of patients with uterine carcinosarcoma which may account for the low disease free survival at one year after adjuvant treatment together with the fact that a large proportion of our patients present with late stage disease. Our study found long waiting times between presentation and treatment with poor follow up by patients. Improved patient education and counselling together with ‘fast tracking’ of oncology patients may be instrumental in better patient adherence and outcomes.

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CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

Cancers of the uterine corpus are the most common Gynaecological malignancies in women in developed countries with an estimated 142 200 new cases and 33 200 deaths annually (1). In contrast the developing world, which comprises roughly 80% of the worlds' population, has a much lower incidence of endometrial cancer (2). Studies in Africa have found endometrial cancer to be the third most common Gynaecological cancer following cervical and ovarian (3, 4). Women in African countries tend to present with late stage disease. In Ghana, almost 20% of women were found to have stage 4 disease at first presentation. These women do not receive adequate treatment due to limited resources further impacting their quality of life and overall survival. As a result the mortality associated with endometrial cancer is greater in African countries than the developed world despite the lower number of cases diagnosed (3). According to GLOBOCAN 2012 there were 167 859 new cases diagnosed in more developed regions with 34 715 deaths compared with 8763 new cases and 3257 deaths reported in Sub-Saharan African (1).

In South Africa, statistics are similar to those of the rest of Africa. The majority of morbidity and mortality results from cervical cancer. Due to the country's high prevalence of Human Immunodeficiency Virus (HIV) and the poor implementation of the national cervical screening programme, the incidence associated with cervical cancer far exceeds that of uterine cancer. In 2009, cervical cancer accounted for 17.6% of all malignancies in South African women. It was the second most common malignancy in South African women with 5270 new cases diagnosed in 2009. Uterine cancer was far less common and accounted for only 3.6% of cancers in South African women and 1073 new cases in 2009. The South

African National Cancer Registry shows an increase in number of new cases of uterine cancer, from 2.6% in 1998 to 3.6% in 2009 (5).

1.2 Classification of Endometrial Cancers

Endometrial cancers were classified into two categories by Bokhman (6) in 1983 according to the presence or absence of hyperoestrogenism and lipid and carbohydrate metabolic disturbances. According to Bokhman, the first group of patients are more likely to have well differentiated tumours arising from hyperplastic endometrial tissue as a result of hyperoestrogenism. These patients are also likely to be obese, diabetic and hypertensive with hyperlipidaemia. The second group develops less well differentiated tumours on a background of atrophic endometrium and has no associated endocrine or metabolic abnormalities (6).

Following the study by Bokhman, further clinicopathological studies have led to the formation of two types of endometrial carcinomas, namely type I and type II (7). Type I tumours are moderately to well differentiated endometrioid adenocarcinomas (Grade 1 and 2) whereas type II tumours include poorly differentiated endometrioid adenocarcinomas (Grade 3) and non endometrioid histological types, uterine papillary serous and clear cell cancers (8). Grade 3 adenocarcinoma is not considered a type I tumour despite being an adenocarcinoma. Due to the aggressive nature of the tumour it is grouped with type II tumours (7).

Uterine carcinosarcomas (Malignant Mixed Mullerian Tumours) were previously grouped as uterine sarcomas due to the sarcomatous element of the tumour. Uterine sarcomas are rare tumours comprising three to seven percent of uterine cancers. Carcinosarcoma was the most common tumour in this group making up about 40% of uterine sarcomas (9).

Carcinosarcoma is now thought to be a dedifferentiated or metaplastic form of endometrial carcinoma (9) and has been reclassified by the International Federation of Gynecology and Obstetrics (FIGO) in 2009 as a type of endometrial carcinoma to be staged as for endometrial carcinoma (10). This reclassification comes due to several reasons. Firstly and most importantly, carcinosarcomas have been shown using immunohistochemical investigations to derive from a single stem cell. They are not composed of independent carcinomatous and sarcomatous parts as previously thought (11). There is concordance between p53 protein expression in both elements of the tumour indicating a monoclonal origin (10). Secondly, carcinosarcomas have been found to share certain risk factors with endometrial adenocarcinomas (11) including obesity, nulliparity and exogenous oestrogen use (10). Lastly, the clinicopathological behaviour of carcinosarcoma is more dependent on the epithelial component; it is the "driving force" of the tumour. The sarcomatous portion has little or no effect on the metastatic potential. Both endometrial adenocarcinoma and carcinosarcoma favour lymphatic dissemination compared with the more common haematogenous spread of sarcomas. The stromal portion of the carcinosarcoma seems to merely be an indicator of increased aggressiveness of the tumour (11).

However, not all researchers agree with this reclassification. A recent Japanese study published in 2012 has found that gene expression profiles of carcinosarcoma are more similar to that of uterine sarcomas (12). Studies by Amant et al and Bansal et al comparing carcinosarcoma and Grade 3 endometrial cancer have reported a far worse prognosis and survival for women with carcinosarcoma. Due to these findings they suggest that carcinosarcoma should be viewed as a "biologically distinct entity" and not be grouped with high risk endometrial carcinomas (11, 13).

1.3 Staging of Endometrial Cancer

The revised FIGO classification of 2009 includes four stages for the classification of endometrial carcinoma including carcinosarcoma. The first stage is confined to the uterus, with either less than 50% myometrial invasion (1A) or more than 50% myometrial invasion (1B) present (2). Stage 2 includes cervical stromal invasion, but no invasion beyond the uterus. Stage 3 and 4 involve disease that has spread beyond the uterus. Stage 3A, tumour invades the serosa of uterus or adnexa, Stage 3B there is vaginal and/or parametrial involvement. Stage 3C is divided into 3C1 which denotes pelvic lymph node involvement and 3C2 for para-aortic lymph node spread. Stage 4 involves bladder and/or rectal mucosa (4A) or distant metastases (4B) which includes spread to inguinal lymph nodes (2).

The staging system for endometrial carcinoma has for the first time in 2009 been separated from that of uterine sarcomas. The two classifications differ somewhat considering the uterine sarcoma staging where only stage 1 is confined to the uterus (2).

As of 1988, the staging of endometrial carcinoma is on surgicopathological not clinical findings, therefore necessitating total abdominal hysterectomy, bilateral salpingooophorectomy and pelvic lymphadenectomy. Accurate staging is an important tool in determining the prognosis of a patient. It also allows for comparison of patient outcomes and aids in decision making in terms of requirements for adjuvant treatment. There were four notable changes in the revision of the staging system in 2009 (14). Firstly, non-invasive tumours and those with less than 50% myometrial invasion (1988 stage 1A and 1B) were combined into stage 1A as these stages showed a similar disease specific survival (14). However, a comparison of 1988 and 2009 staging of stage 1 tumours done by Abu-Rustum et al concluded that the revised system did not improve the prognostic predictability for stage 1 disease (15).

Secondly, cervical glandular involvement no longer affects the staging. This effectively converts 1988 stage 2A into 2009 stage 1A/B and was done due to the fact that previously stage 2A patients had a better survival over stage 1C (2). Thirdly, peritoneal cytology does not affect staging in the 2009 classification. Several studies have shown no association between positive peritoneal cytology and survival or recurrence of disease. For this reason peritoneal washings were dropped in the 2009 revision (14). However, according to a study by Haltia et al, positive peritoneal washings should still be considered as a poor prognostic sign (14).

The last alteration to the staging is in stage 3C denoting lymph node involvement. According to the 2009 classification it is divided into subcategories 3C1 for pelvic lymph nodes and 3C2 for para-aortic lymph nodes. Considering the differing five year survival rates for stage 3C1 of 57% versus 47% for stage 3C2, this differentiation allows for improved prognostic accuracy (16).

1.4 Risk factors

1.4.1 Type I Tumours

Risk of type I tumours is linked to early menarche, late menopause, nulliparity and all conditions associated with unopposed oestrogen exposure. Obesity, which causes higher circulating levels of oestrogen, together with postmenopausal use of oestrogens has been shown to increase the incidence of type I endometrial carcinoma (7, 17). In South Africa, obesity as a risk factor is an important concern considering the rate of obesity in South African women. According to the South African Demographics and Health Survey in 2003, the proportion of obese adult women was 27.4% and overweight 27.5% (18). These high

rates of obesity can lead to higher rates of oestrogen related malignancies, particularly the development of type I endometrial cancer (19).

The Metabolic syndrome has become a major public health problem particularly in areas with high incidence of obesity (20). Significant positive associations have been found between the presence of the Metabolic syndrome and endometrial cancer. However, these studies identify obesity as the single most important component associated with development of endometrial cancer, further underlining its importance as a carcinogenic factor (20, 21).

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age. The prevalence varies between six and ten percent depending on the diagnostic criteria used. The syndrome is associated with long term health problems namely cardiovascular disease, metabolic disorders and development of cancer (22, 23). As with obesity, the risk of developing endometrial cancer stems from the chronic anovulatory state and exposure to unopposed oestrogen resulting in endometrial hyperplasia and malignant changes (24). Recent studies have confirmed this association and shown a four fold increase in risk of developing type I endometrial cancer for women with PCOS (22). Women of all ages are affected but this risk may be further elevated in the premenopausal subgroup (23).

1.4.2 Type II Tumours

In contrast, type II tumours have been shown to have different risk factors. Multiparity and smoking which are protective factors for type I tumours confer an increased risk for type II tumours. Postmenopausal status and tamoxifen use are also important in the development of type II tumours (7). Carcinosarcoma appears to share risk factors with both type I and II tumours therefore obesity, smoking as well as increasing parity can increase the risk of carcinosarcoma (11). This difference in risk factors adds to the argument that there are

completely different pathological processes involved in the development of type I and II tumours (7).

1.4.3 Protective Factors

Protective factors for type I tumours include oral contraceptive use, increasing parity and smoking (25). Oral contraceptives can decrease the risk of endometrial cancer by 80% with more than ten years use and the protective effect continues for over twenty years after stopping treatment (26). A South African study by Urban et al, demonstrated a significantly lower risk of endometrial cancer in women using oral or injectable contraceptives for more than five years (OR 0.44, CI 0.22-0.86, p=0.02) (27). Increasing parity has a protective effect, which is stronger in the premenopausal than post-menopausal woman (26).

1.4.4 Tamoxifen Use

Tamoxifen is a selective oestrogen receptor modulator currently used with good effect in the treatment of oestrogen receptor positive breast cancer. It has been found that tamoxifen has different effects on breast and endometrial tissue. In the breast, tamoxifen has an anti-oestrogenic effect and restricts the growth of breast tissue, however, in the endometrium pro-oestrogenic effects promote the growth of tissue leading to endometrial hyperplasia and cancer (8). Since the first published report by Fornander et al in 1989, multiple studies have demonstrated this increased risk of endometrial neoplasia (28). A systematic review on tamoxifen in early breast cancer put together by the Early Breast Cancer Trialists' Collaborative Group reported a two and a half times greater risk of developing endometrial cancer after taking tamoxifen. This risk further increases with duration of use (29).

Silva et al and Magriples et al both demonstrated a higher proportion of type II tumours developing in women treated with tamoxifen than those who did not receive tamoxifen (30, 31). This increased risk is more pronounced with women receiving tamoxifen for more than sixty months (32). Women have been found to develop type I tumours during tamoxifen treatment whereas type II tumours are more likely to develop years after stopping tamoxifen. This would suggest that there is a different pathogenesis in the development of type I compared to type II tumours following tamoxifen exposure (28). Lastly, several authors have reported a significant increase in development of carcinosarcomas with tamoxifen use (8, 33). Curtis et al reported a four fold relative risk for carcinosarcoma which increased to eight fold if tamoxifen was continued for more than five years (33). Patients treated with tamoxifen have been found to have similar overall survival to those with no previous tamoxifen use (32).

1.4.5 Radiation Exposure

Radiation therapy has been linked to an increased risk of endometrial cancer, although the actual number of women found to have endometrial cancer following radiation therapy is very low. One retrospective review by Pothuri et al identified 23 women with radiation associated endometrial cancer compared with 527 women with sporadic endometrial cancer over 24 year period in two major cancer centres (34). These women, who underwent radiation therapy for cervical carcinoma, were more likely to develop high risk tumours, carcinosarcomas or type II endometrial carcinomas, compared with women who developed sporadic cancers. Thirty five percent developed carcinosarcoma which was much higher than the sporadic incidence of carcinosarcoma of six percent. The researchers also found that the women who had previously received radiation therapy had poorer outcomes and shorter overall survival compared to those with sporadic endometrial cancer (34).

1.5 Demographic Factors

1.5.1 Age

Endometrial carcinoma is mainly a disease of older women with a median age of 61 years and more than 50% of women are diagnosed between the age of 50 and 69 years (2). Patients with carcinosarcoma tend to be older with a mean age at diagnosis of 67 years (17). Older age is associated with a higher risk of recurrence and a worse overall survival (12).

1.5.2 Race

Numerous previous studies have focused on racial discrepancies in endometrial cancer. Differences have been observed between black and white women in terms of demographics, prognosis and overall survival. Reviews of the SEER database by Wright et al have shown that significantly less black women are diagnosed with endometrial cancers but there are more deaths from endometrial cancer in black than white women (35). Incidence of endometrial cancer in black women is 30% lower than white women but the mortality rate is 80% higher (36).

Black women tend to be diagnosed at a younger age than white women (37), they present with more advanced disease (35, 38) and are three times more likely to have a high risk type of endometrial carcinoma or a carcinosarcomas (36, 39). Black women also have lower survival rates for early stage disease and low risk subtypes which usually carry a more favourable outcome (25, 36). All together these factors contribute towards a poorer prognosis and overall survival in black women.

Several authors have suggested these differences may be due to inequalities in access to health care and differences in the level of care received by black and white women (35, 38).

A study conducted by Oliver et al looking at women managed in Military treatment facilities found that older black women were more likely to have higher disease stages and tumour grades at presentation, and more aggressive histological types than white women (40). This contributed to their poorer prognosis and survival. This study population was considered to be an equal access healthcare population as healthcare did not depend on socioeconomic status. The authors' felt that these results underlined the presence of an inherent difference between black and white women where access to health care is not an obstacle (40). Despite these findings, the majority of black patients in the United Stated are of lower income groups which often equates to poorer outcomes (41). The reason for the discrepancy in survival is more likely to be multifactorial (36).

1.5.3 Socioeconomic Status

Socioeconomic status has been found to be influential in prognosis of women with low grade tumours at early stages of disease. Patients with higher incomes are more likely to consult earlier and have a hysterectomy; improving their chances of a good outcome. Socioeconomic factors are far less important when considering high risk endometrial tumours at advanced stages of disease. When outcomes of women with advanced disease have been compared in terms of histological type, race and median family income were not associated with an improved prognosis (41).

1.6 Patient Characteristics

1.6.1 Medical Conditions

A study by Olson et al compared prevalence of comorbidities in black and white women with endometrial cancer (42). Women with comorbidities were more likely to receive chemotherapy than surgery and radiation therapy as their medical conditions precluded them from anaesthesia. As a result of less aggressive management and worse health status these patients had poorer outcomes. Diabetes was shown to have a negative effect on overall survival, however, hypertension had a positive effect on survival in black women. The presence of other comorbidities was found to affect overall survival of women but had no effect on disease specific survival (42).

1.6.2 Human Immunodeficiency Virus (HIV)

In South Africa there are an estimated 6.1 million people living with HIV/AIDS of which 3.4 million are women of 15 years and older (43). Unlike cervical cancer, which is an AIDS defining condition, there is no definite link between HIV and endometrial cancer. However, several case reports have been published documenting patients with endometrial cancer and HIV. These patients have demonstrated surprisingly aggressive disease. The authors have posed the question as to whether the co-infection of HIV resulted in the unusual and aggressive behaviour of the tumour or whether the interaction with antiretroviral therapy altered the presentation or course of the disease (44).

1.7 Management

1.7.1 Surgical Management

Standard surgical management includes a Total Abdominal Hysterectomy and Bilateral salpingooophorectomy. For patients with papillary serous and clear cell tumours, infracolic omentectomy should also be done (19).

Lymphadenectomy is a controversial part of surgical management for endometrial cancer. Dissection of pelvic lymph nodes allows for more accurate staging and therefore a better indication of prognosis. However, it can be technically difficult to perform and associated with significant long term morbidity (16).

The incidence of pelvic lymph node metastases increases with the depth of myometrial invasion therefore very few women with stage I disease will have metastases to the pelvic lymph nodes. The ASTEC trial conducted in the United Kingdom showed no benefit of lymphadenectomy on overall or disease free survival in women with early endometrial cancer (19).

Lymphadenectomy can provide information to be used in the planning of adjuvant therapy. Access to radiotherapy is often difficult in South African centres due to a lack of equipment and high patient loads. By carrying out a lymph node dissection for high risk patients, those patients with lymph node positive disease can be better identified. Radiotherapy time and resources can be saved on those who are lymph node negative (19). However, at the same time, patients with early stage (lymph node negative) high risk disease have been found to have lower recurrence rates following radiotherapy (16).

Possible complications of lymphadenectomy during surgery include blood loss, nerve damage and prolonged operating time. Long term, patients may suffer from lymph oedema following removal of pelvic lymph nodes. The exact lymphatic drainage of the uterus is difficult to pin point and some authors advocate extensive dissection beyond the pelvis which has added surgical risks. Taking this into consideration, lymph node dissection had no

'therapeutic advantage' for patients with early stage disease but evidently has a survival benefit for patients with disease of stage II or greater (16, 19).

With regards to carcinosarcoma, surgery is the primary treatment modality and pelvic lymphadenectomy is an important part of the staging. Particularly considering that up to 60% of patients will have metastases present with tumours confined to the uterus. Most studies have shown a therapeutic advantage to lymph node dissection in all stages of disease (45). Cytoreductive surgery with no gross residual disease has shown a significantly better overall survival (25 months with no residual disease vs 13 months with residual disease) (45).

In keeping with current literature and study findings, the protocol according to University of Witwatersrand Gynaecology oncology unit is to perform Total Abdominal Hysterectomy, Bilateral Salpingooophorectomy and routine lymphadenectomy for all patients found to have a high risk histological subtype on preoperative work up. Patients with low risk tumours do not have routine lymphadenectomy. For patients with carcinosarcoma lymph node biopsy is done when indicated (46).

1.7.2 Adjuvant Therapy

The use of adjuvant radiotherapy is dependent on the staging of the patient. Several studies have shown no survival benefit of employing radiotherapy in patients with stage 1 endometrial cancer therefore it is not recommended in stage 1 disease. However, patients with high risk stage 1 disease (G3 or type II tumours) have shown lower recurrence rates compared to those who did not receive postoperative radiotherapy (16).

Radiotherapy is recommended in patients with stage 2 to 4 endometrial cancer as studies have shown improvement in local recurrence rates with whole pelvic or extended field radiotherapy compared to surgery alone (19).

Radiotherapy is indicated for all stages of carcinosarcoma but there is currently no consensus as to the ideal mode of adjuvant therapy. Either pelvic irradiation or brachytherapy has been shown to decreases the local recurrence rate of carcinosarcoma but in many studies this does not translate into an improved overall survival particularly in patients with stage 1 disease. In contrast a SEER data base study showed improved overall survival of 56% compared to 50.8% with no radiotherapy (45).

Radiotherapy is offered (and given) to all patients treated for endometrial carcinoma and carcinosarcoma at Charlotte Maxeke Johannesburg Academic Hospital except for stage 1 endometrial cancer with low risk tumours, as per the University of Witwatersrand protocol (46).

There is little evidence on the use of chemotherapy in early stage endometrial cancer (16) but in recent years the use of chemotherapy has become a more accepted option for the treatment of high risk, advanced endometrial cancer (19). There appears to be a better overall survival rate for women receiving chemotherapy compared to radiotherapy. A study done by Randall et al comparing whole abdominal irradiation and combination chemotherapy (doxorubicin/cisplatin) for stage 3 and 4 endometrial cancer showed a five year disease free survival of 38% and 50% respectively (19). Side effects, toxicity and a temporary reduction in quality of life may be factors limiting the use of chemotherapy in all patients with advanced or high risk disease (47).

Chemotherapy has been shown to be effective in the treatment of carcinosarcoma with combination ifosfamide/cisplatin or ifosfamide/paclitaxel being more effective than single

agent ifosfamide. There are no prospective randomised controlled trials comparing chemotherapy regimens and multiple agents are often associated with high levels of toxicity (45).

Multimodal treatment regimens or the so called “Sandwich” method have been used in the treatment of both high risk endometrial carcinoma and carcinosarcoma. There is currently little consensus as to the appropriate chemotherapy agents and treatment spacing to be used but limited data appears to support the technique. Further studies are needed to determine the optimal chemotherapeutic agents, sequencing of treatment modalities and patient populations (45, 48).

1.7.3 Hysteroscopy

Hysteroscopy is a useful modality in diagnosis of intrauterine structural pathology and has the added advantage of allowing for intervention or biopsy at the same time. It is a procedure that can be done as an outpatient and does not require general anaesthetic. There is good accuracy in diagnosing endometrial hyperplasia and cancer on biopsy (49).

Hysteroscopic endometrial resection combined with adjuvant therapy with progesterone is an alternate option for younger patients who have not completed their family. It is a conservative fertility sparing option that has shown good results in terms of cure and pregnancy rates in early stage endometrial cancer and atypical endometrial hyperplasia (50).

Hysteroscopic resection may also be an option for severely compromised patients who cannot withstand general anaesthetic or extensive surgery. Laframboise et al reported a case study where this procedure was combined with high dose rate brachytherapy. However, it is

difficult to gauge the exact benefit of the hysteroscopic resection compared to brachytherapy alone. Further studies are required to determine this (51).

Hysteroscopy is not routinely done as part of investigations for patients with postmenopausal bleeding or abnormal uterine bleeding in premenopausal women at RMMCH. Its use is limited by the cost of equipment and amount theatre time required. The procedure is usually only performed where endometrial sampling is inconclusive or cannot be performed.

1.8 Outcome

The prognosis for endometrial cancer covers a broad spectrum. Patients diagnosed with early stage, low risk tumours have a very favourable outcome of over 95% five year survival given the correct treatment (2). In contrast high risk tumours together with carcinosarcomas have a considerably poorer prognosis especially if diagnosed with stage 3 or 4 disease (38). Study by de Jong et al puts five year survival for carcinosarcoma at 42% compared with 77% for Grade 3 endometrioid adenocarcinoma and 57% for type II cancers (52). The most important prognostic factors in endometrial cancer include stage of disease and amount of residual tumour following surgery as well as tumour histology and grade (12, 35). Advanced age of the patient and African race has also been associated with poor outcome, especially in women with carcinosarcoma (35).

The rate of five year survival is often used as a bench mark for comparison of treatment modalities. However, overall survival is not always disease free and the disease free or recurrence free interval is often a better indication of patient quality of life during their survival. The disease free interval for carcinosarcoma is far poorer than that of endometrial carcinoma (10) with a median time for treatment to recurrence of 13 months for

carcinosarcoma (12). A study by Voss et al found little difference in recurrence free survival between Grade 3 endometrioid adenocarcinoma and type II tumours. Mean disease free survival was found to be 4.7 years and recurrence free survival 4.5 years (53). Recurrence free survival is superior when adjuvant treatment is given compared with no adjuvant treatment and age is significantly associated with risk of tumour recurrence (12).

The incidence of endometrial carcinoma has remained relatively stable but the number of reported deaths per year has doubled since the 1980's. The reason for this is most likely multifactorial, including an increase in more aggressive histology, patients presenting with more advanced stages of disease, poor access to appropriate treatment or improper staging at initial diagnosis (38). The National Cancer Institutes' Surveillance, Epidemiology and End Results (SEER) database is a population based cancer registry in the United Stated of America. A review of the database from 1988 to 2004 by Wright et al shows a gradual increase in uterine papillary serous and clear cell tumours. These two high risk tumours associated with higher mortality have increased by almost two percent in white women and roughly five percent in black women over this sixteen year time period (35).

1.9 Waiting Times

1.9.1 Presenting symptoms

More than 95% of the patients diagnosed with endometrial cancer are symptomatic. The majority of these patients experience abnormal uterine bleeding (2). Pirog et al found that 90% of patients present with abnormal uterine bleeding and 81% have postmenopausal bleeding (54). As patients are symptomatic the majority of them present early and are

diagnosed at an early stage. For the remaining five percent who are asymptomatic, diagnosis is usually as a result of an incidental finding on pap smear or other investigation (2).

1.9.2 Delays in Diagnosis

Diagnosis is confirmed with histological specimen usually via pipelle endometrial biopsy done as an office procedure. However, pipelle biopsy can sometimes be inadequate or inaccurate which may necessitate Hysteroscopy and Diagnostic Dilation and Curettage (DD&C) in theatre. Waiting times for procedures in theatre are far greater than those for out-patient procedures leading to a greater diagnostic delay in patients requiring Hysteroscopy and DD&C (55). In New Zealand, Kang et al found seven percent of patients required Hysteroscopy and DD&C due to inadequate endometrial sampling by pipelle (55).

1.9.3 Delays in treatment

Studies in women suffering from cancers of breast, rectum and bladder have all shown a link between increased treatment delay and poorer overall outcome (56). There appears to be conflicting evidence in women with endometrial cancer. A study by Menczer et al published in 1995 looked at outcomes of 204 women with endometrial cancer. They concluded that a delay in treatment should be avoided whenever possible, but if the delay was less than four months it was not likely to compromise the patient outcomes (57). Crawford et al in 2002 found an inverse relationship. The longer a patient waited for treatment, the more likely they were to survive. This is thought to be because patients with more advanced disease are prioritised and referred to specialists more quickly. They underwent surgery or adjuvant therapy more quickly but due to the advanced stage of disease they did not survive very long following treatment (58).

A recent Canadian study by Elit et al published in January 2014 involving over 4000 patients showed a significantly worse overall survival in patients waiting more than 12 weeks from diagnosis to treatment compared to those waiting between two and 12 weeks. They concluded that treatment, either surgery or radiation, should take place within two to six weeks of diagnosis to optimise survival. They also found that patients waiting less than two weeks for treatment had a poorer overall survival. This was thought to be due to more advanced disease and more aggressive tumours as well as complications associated with emergency procedures taking place afterhours or on weekends (56).

Delays in diagnosis and treatment can be patient or health system related. Poor patient knowledge as to the signs and symptoms of cancer may lead to a delay in presentation to health centres. Patients may have multiple comorbidities requiring additional workup before surgery (59). They may also default appointment or refuse surgical procedures. Health system delays are usually related to lack of theatre time or expertise in management of oncology patients (55).

CHAPTER 2: AIMS OF STUDY

2.1 Aims

The literature has shown that African American women are diagnosed at a younger age, have a higher incidence of type II tumours and carcinosarcoma and have worse overall survival than white women. This study aims to identify the presence of risk factors, the incidence of histological types and initial treatment outcomes of endometrial cancer in women in a South African hospital in order to determine whether results are in keeping with international data.

Tertiary level government hospitals in Johannesburg and Gauteng serve a large geographical area with multiple clinics and district hospitals referring patients with gynaecological conditions. Gynaecological Out Patient Departments are therefore often very busy with long waiting times before consulting a doctor and long waiting lists for surgical procedures. There is also a significant delay in obtaining histology results following investigations or surgery as the National Health Laboratory Service has large volumes of specimens to process and limited qualified staff. This can result in delays in management of patients. This study also aims to determine how long it takes from initial presentation of the patient at Rahima Moosa Mother and Child Hospital until diagnosis and treatment at the department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital. This study aims to identify the presence of delays in patient care and whether it is possible to streamline the process.

2.2 Objectives

2.2.1 To determine the stage of disease at which most patients present.

2.2.2 To determine the proportion of different histological types of endometrial cancer and carcinosarcoma.

2.2.3 To determine the presence of significant risk factors in women with endometrial cancer and carcinosarcoma.

2.2.4 To describe the demographics of patients diagnosed with endometrial cancer at Rahima Moosa Mother and Child Hospital.

2.2.5 To describe the treatment received by women and the outcome after follow up of one year.

2.2.6 To compare the demographics, risk factors, stage at presentation and outcomes of patients with endometrial cancer and carcinosarcoma.

2.2.7 To establish the average length of time between initial presentation and treatment of the patient.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This is a retrospective descriptive study of women newly diagnosed with endometrial cancer or carcinosarcoma at Rahima Moosa Mother and Child Hospital (RMMCH) from 2009 to 2013. All women presenting with a gynaecological cancer at RMMCH are investigated and undergo surgery if required. Patients undergo Total Abdominal Hysterectomy and Bilateral Salpingooophorectomy, omentectomy and peritoneal washings. No lymphadenectomy is done. Once histological diagnosis is confirmed they are referred for presentation at the combined oncology meeting at Charlotte Makexe Johannesburg Academic Hospital (CMJAH). Depending on the stage of disease and type of tumour present the women either receive radiotherapy or are followed up only. A register of these patients is kept at RMMCH detailing their diagnosis, stage of disease and plan for further treatment. Women diagnosed with endometrial cancer were identified from this register and their full records obtained for review. Patient records are kept at RMMCH for a limited time period before they are destroyed therefore dictating the study interval of 2009 to 2013. Records from the Radiation Oncology department at CMJAH were also reviewed in order to obtain information regarding treatment received at CMJAH and patient well-being one year after treatment.

3.2 Study Setting

Rahima Moosa Mother and Child Hospital is a regional level hospital located in Coronationville, Johannesburg. The hospital provides Obstetric and Gynaecological services and caters to the surrounding areas. It is the referral hospital for clinics and district hospitals in the western Johannesburg region. Women diagnosed with any kind of Gynaecological

cancer are staged and then referred to CMJAH Oncology department for further treatment. CMJAH is a tertiary level hospital that provides oncology services for all cancer patients in the greater Gauteng area.

3.3 Study Population

Women diagnosed with endometrial cancer and carcinosarcoma. Women of any age or ethnicity provided that they have been diagnosed with endometrial cancer or carcinosarcoma originating in the uterus. This must be an index presentation and not a recurrence after previous treatment.

3.4 Literature Review

The literature search was conducted via Pubmed using the key words: endometrial cancer, uterine carcinosarcoma, endometrial cancer management, waiting times, treatment delays.

Relevant references were accessed if available via the University of the Witwatersrand eJournal portal. Appropriate articles cited by other authors were also reviewed. Appropriate websites were also used and referenced.

3.5 Data Collection

Data was obtained from patient files. Files from both RMMCH Gynaecology department and CMJAH Radiation Oncology department were obtained for review. Information collected included age, race, parity, gravidity, menarche, menopause, weight, contraceptive use, medical history, medication use, HIV status, smoking, presenting symptoms, investigations

done, histology, staging, treatment received, outcome at one year and time intervals (Appendix 8.1 Data Sheet).

3.6 Data Analysis

Descriptive tables were constructed for socio-demographic characteristics and for factors thought to be associated with cancer stage and histology result. Means, medians and ranges were described for continuous variables. Categorical variables were tabulated and their frequencies were recorded. We used one-way ANOVA test, the Kruskal-Wallis test (for data that was not normally distributed) and chi-square (using Fischer's exact where appropriate) to determine factors associated with cancer stage and histology result.

3.7 Ethics Approval

The research protocol was submitted and approved by the WITS Human Research Ethics Committee, reference number: M130861.

CHAPTER 4: RESULTS

4.1. Sample Population

A total of 59 patients were identified as having been diagnosed with endometrial cancer at Rahima Moosa Mother and Child Hospital between 2009 and 2013. Hospital records were available for 55 out of the 59 patients (93.2%). Of the 55 patients from RMMCH, 50 of them were presented at CMJAH Oncology department for further treatment. Five patients did not follow up after surgery and were not presented at CMJAH. CMJAH oncology records were available for 47 out of the 50 patients. Of these 47 patients, 12 required only follow up and no further treatment, 24 received radiation therapy, four were referred to the Chemotherapy department, six patients defaulted before receiving treatment and one patient died before receiving treatment. Of the 24 patients who received radiation therapy, four patients defaulted after their first treatment.

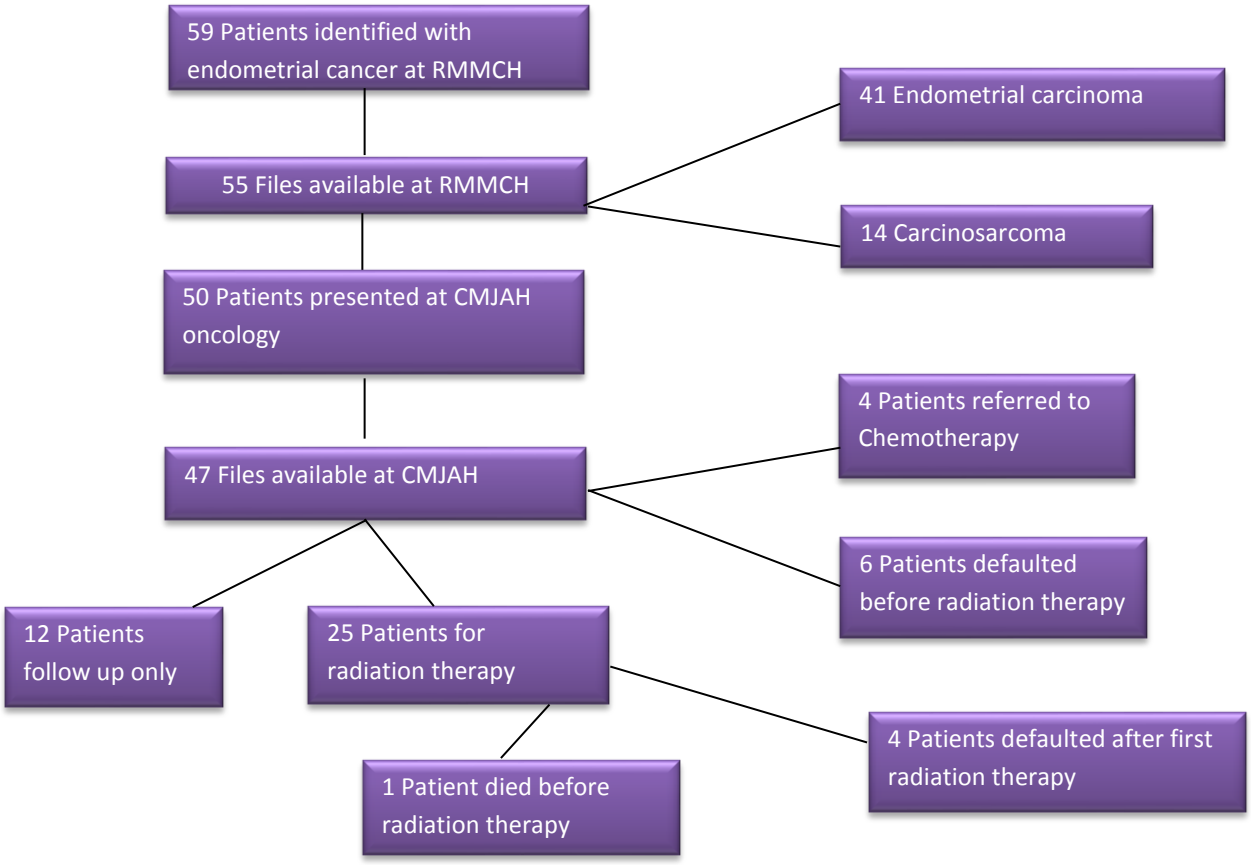


Figure 4.1 Flow diagram of sample population

Of the 55 patients, 41 (74.5%) had endometrial carcinoma and 14 (25.4%) had carcinosarcoma. Of the patients with endometrial carcinoma, 19 (34.5%) were low grade adenocarcinoma, 13 (23.6%) were high grade adenocarcinoma, seven (12.7%) were papillary serous carcinoma, one (1.8%) was clear cell carcinoma and one (1.8%) was an unspecified endometrial carcinoma.

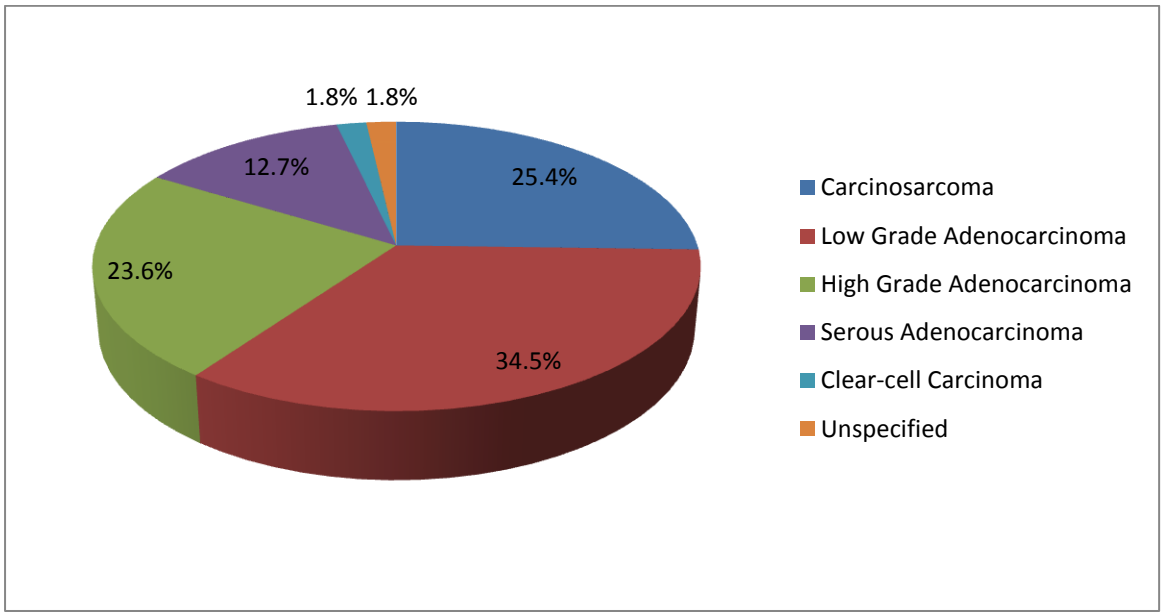


Figure 4.2 Histological types

For the patients with endometrial carcinoma, 27 (65.8%) patients were in stage 1 or 2 and 14 (34.1%) were stage 3 or 4. For the patients with carcinosarcoma, four (28.5%) were in stage 1 or 2 and ten (71.4%) were in stage 3 or 4. There were six patients with endometrial carcinoma presenting in stage 4. Site of metastases included bladder, liver, lungs, kidney and two patients with omental deposits. Site of metastases in patients with carcinosarcoma included bladder and omentum.

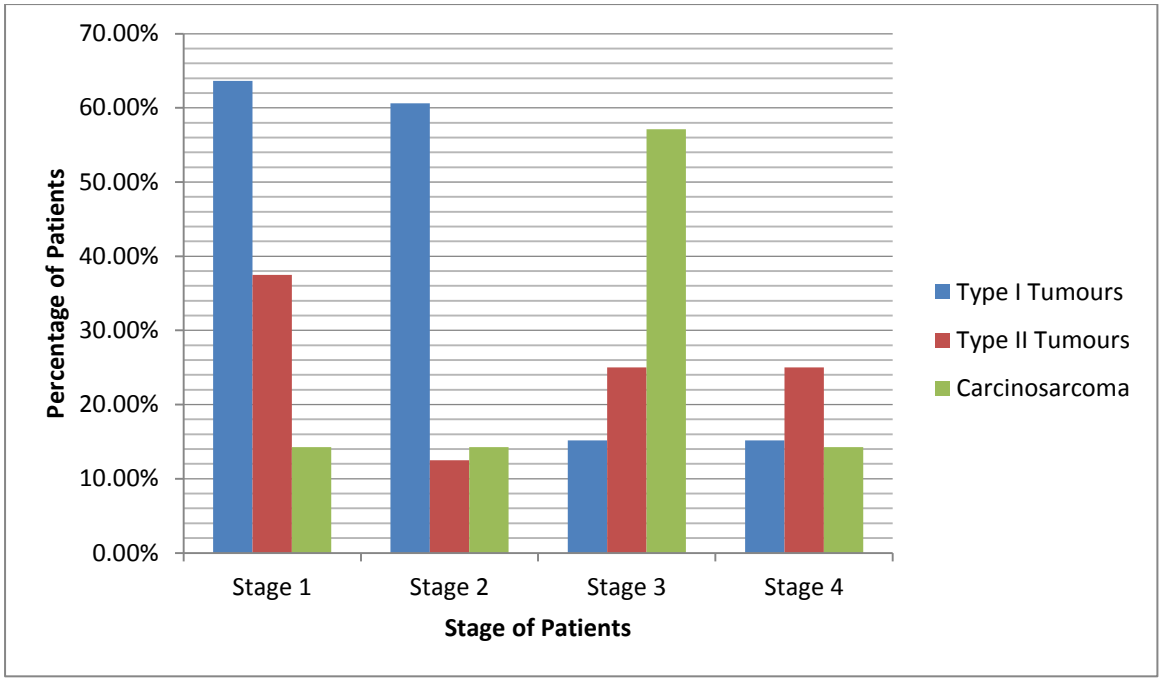


Figure 4.3 Stage at diagnosis

4.2. Risk factors

4.2.1 Menarche

Data for menarche was available for 45 patients and data was missing for ten patients. The age range for menarche was ten to 18 years, with a mean of 14.3 years and median of 15 years. 54.3% of patients with endometrial carcinoma and 50.0% of patients with carcinosarcoma reached menarche at 15 or more years of age, compared with only 14.3% and 12.5% of patients who were 12 years or less of age. There was no association between age at menarche and histology and stage of cancer (p=0.32, p=0.87 respectively).

4.2.2 Menopause

There were 50 patients who were postmenopausal, five patients were pre or perimenopausal. Data was missing for three of the 50 postmenopausal patients. The age range for menopause

was 33 - 60 years, with a mean of 53.3 years and median of 52 years. Mean age at menopause for patients with endometrial carcinoma was 51.8 years and 49.4 years for those with carcinosarcoma. The mean length of time that a woman had been postmenopausal was 13.7 years for endometrial carcinoma and 17.8 years for carcinosarcoma. There was no association between menopausal status or age at menopause and histology (p=0.90 and p=0.87 respectively).

4.2.3 Parity

Patients with endometrial carcinoma had a median parity of three. Patients with carcinosarcoma had a median parity of four. Only six patients (14.6%) with endometrial carcinoma and one patient (7.1%) with carcinosarcoma were nulliparous, whereas 30 (73.2%) and 12 (85.7%) patients respectively were multiparous (two or more births). There was no association between parity and histology (p=0.18).

4.2.4 Gravidity

Patients with endometrial cancer had a median gravidity of four. The patients with carcinosarcoma had a median gravidity of four. Only five patients (12.2%) with endometrial carcinoma and one (7.1%) with carcinosarcoma had never been pregnant. More than 75% of patients with both endometrial carcinoma and carcinosarcoma had had two or more pregnancies. There was a positive association between gravidity and histological grade (p=0.04).

	EC	CS
Gravidity <1	9	1
Gravidity ≥1	32	13

Table 4.1 Patient gravidity and histological grade

4.2.5 Patient weight

Patients' weight was recorded for 41 patients. The mean patient weight was 81.5 kilograms with median weight of 83 kilograms and range of 38 - 123 kilograms. 24 out of 41 patients (58.5%) had a weight of greater than 80 kilograms. Height was only available for 16 patients thus allowing for calculation of BMI in these 16 patients. The mean BMI was 33kg/m^2 with a range of 22 – 56 kg/m^2. Ten out of 16 patients (62.5%) had a BMI greater than 30kg/m^2. There was no association between patient weight or BMI and histology or stage of cancer.

4.2.6. Hormone Replacement Therapy (HRT)

Only one out of 41 patients diagnosed with endometrial carcinoma had previously taken HRT. The duration and type of treatment taken was unknown for this patient, as well as the time interval since stopping treatment until presentation. Data was missing for two patients with carcinosarcoma but none of the other patients with carcinosarcoma had a history of HRT use.

4.2.7 Tamoxifen

Only one patient with endometrial carcinoma had a previous history of having taken tamoxifen. The indication for use was breast cancer and duration of treatment was unknown.

The time interval between stopping use and presentation was also unknown. None of the patients with carcinosarcoma had previously taken tamoxifen. There was no association between histology and tamoxifen (p=0.70).

4.2.8 Hormonal Contraceptives

There were 11 patients (20.0%) who had previously used hormonal contraceptives (either oral or injectable contraceptives), 40 patients (72.7%) who had not used any hormonal contraceptives and four patients had missing data. Eight of the 11 patients (72.7%) were diagnosed with endometrial carcinoma and three of the 11 patients (27.3%) were diagnosed with carcinosarcoma. The duration of use was unknown for seven patients. Of the remaining patients the duration of use was two months, two months, eight months and five years respectively. There was no association between stage of cancer or histology and hormonal contraceptives (p=0.20).

4.2.9 Smoking

There were 50 patients (90.9%) who were non-smokers and five patients (9.1%) who reported ever smoking. These five patients were all diagnosed with endometrial carcinomas (two low grade endometrioid, two high grade endometrioid and one papillary serous carcinoma). There was no association between ever smoking and histology (p=0.78).

4.2.10 Previous history of cancer

None of the patients with carcinosarcoma had a previous history of cancer. Only one of the patients with endometrial carcinoma had a history of breast cancer. There was a significant

association between previous history of cancer and stage of cancer using Fischer's exact test (p=0.012).

	Stage I/II	Stage III/IV
Previous History of Cancer	1	0
No Previous History of Cancer	30	24

Table 4.2 Previous history of cancer and stage of cancer

4.2.11 Radiation therapy

No patients had received previous radiation therapy.

4.3. Demographic factors

4.3.1 Age

The mean age of patients with endometrial carcinoma was 62.9 years, the median was 63 years and the range 36 to 85 years. The mean age for patients with carcinosarcoma was 68.4 years, the median was 69 years and the range was 52 to 84 years. In the carcinosarcoma group there was only one woman less than 60 years and 92.8% were more than or equal to 60 years. In the endometrial carcinoma group 87.8% of patients were more than or equal to 55 years.

4.3.2 Race

There were 38 (69.1%) black patients, five (9.1%) coloured patients, six (10.9%) asian patients and six (10.9%) white patients. Of the black patients 28.9% had carcinosarcoma,

60.5% had type I tumours and 10.5% had type II tumours. Of the white patients 16.6% had carcinosarcoma, 66.6% had type I tumours and 16.6% had type II tumours.

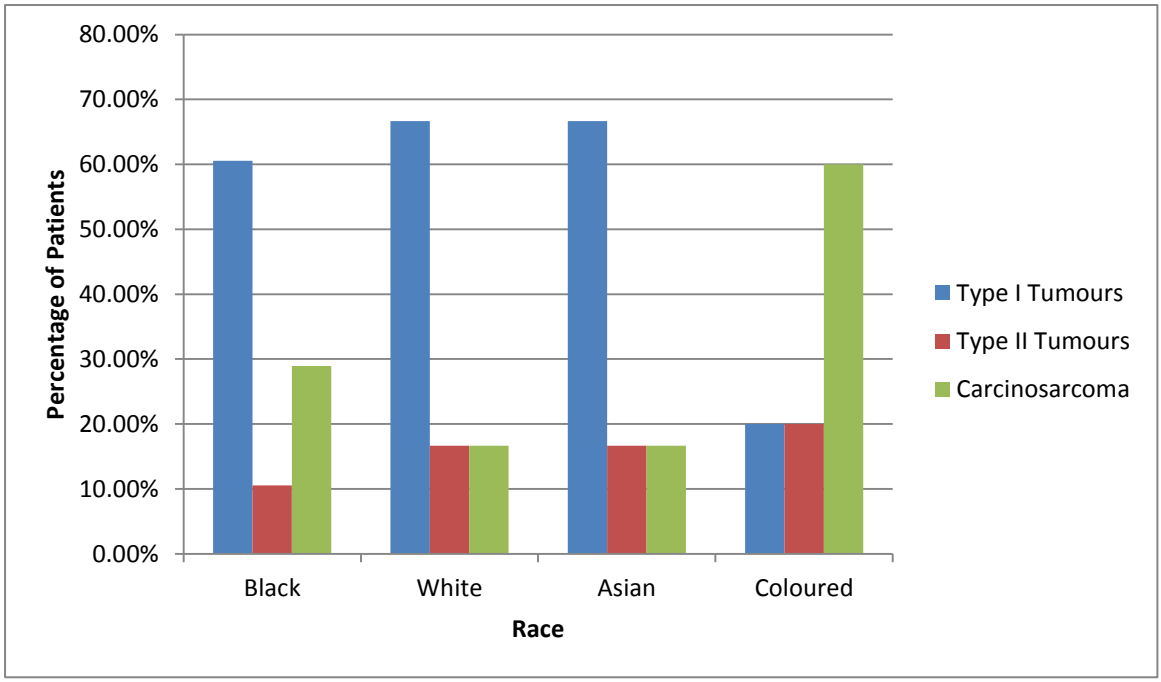


Figure 4.4 Histological type according to race

4.4. Patient Characteristics

4.4.1 Medical conditions

4.4.1.1 Diabetes

There were eight patients (14.5%) with Diabetes Mellitus (five with endometrial carcinoma and three with carcinosarcoma). All of them were type 2 diabetics receiving oral hypoglycaemics.

4.4.1.2 Hypertension

There were 40 patients (72.7%) with hypertension (70.7% with endometrial carcinoma and 78.5% with carcinosarcoma), all of whom were taking antihypertensives. There were 21

patients (38.2%) taking one drug, 14 patients (25.5%) taking two drugs and three patients (5.5%) taking three or more drugs.

4.4.1.3 Other medical conditions

There were 12 patients (21.8%) with medical conditions other than hypertension or diabetes. Some suffered more than one condition, these included asthma, chronic obstructive pulmonary disease, congestive cardiac failure, chronic renal failure, osteoarthritis, hypercholestrolaemia and hypothroidism.

4.4.2 HIV

There were 51 patients (92.7%) who were HIV negative and four patients (7.3%) who were HIV positive. Of the four HIV positive patients three developed endometrial carcinoma. Their CD4 counts were 129 and 345 cells/mm^3 respectively with one value unknown. Only one of these patients was taking antiretroviral therapy. There was one HIV positive patient with carcinosarcoma. Their CD4 count was 595 cell/mm^3 and they were not on any antiretroviral therapy.

4.5. Treatment received and outcomes after one year

There were 47 patients who underwent simple Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy. No lymphadenectomy was done. Following surgery the patients with stage 2 and higher were referred for radiotherapy. Inoperable patients and those with poor health due to medical conditions were referred to CMJAH for primary radiotherapy. They received either whole pelvic irradiation or brachytherapy depending on their staging.

Four patients were referred to the Chemotherapy department and did not receive radiation therapy. The decision as to which adjuvant treatment would be offered to a patient was made at the combined oncology meeting.

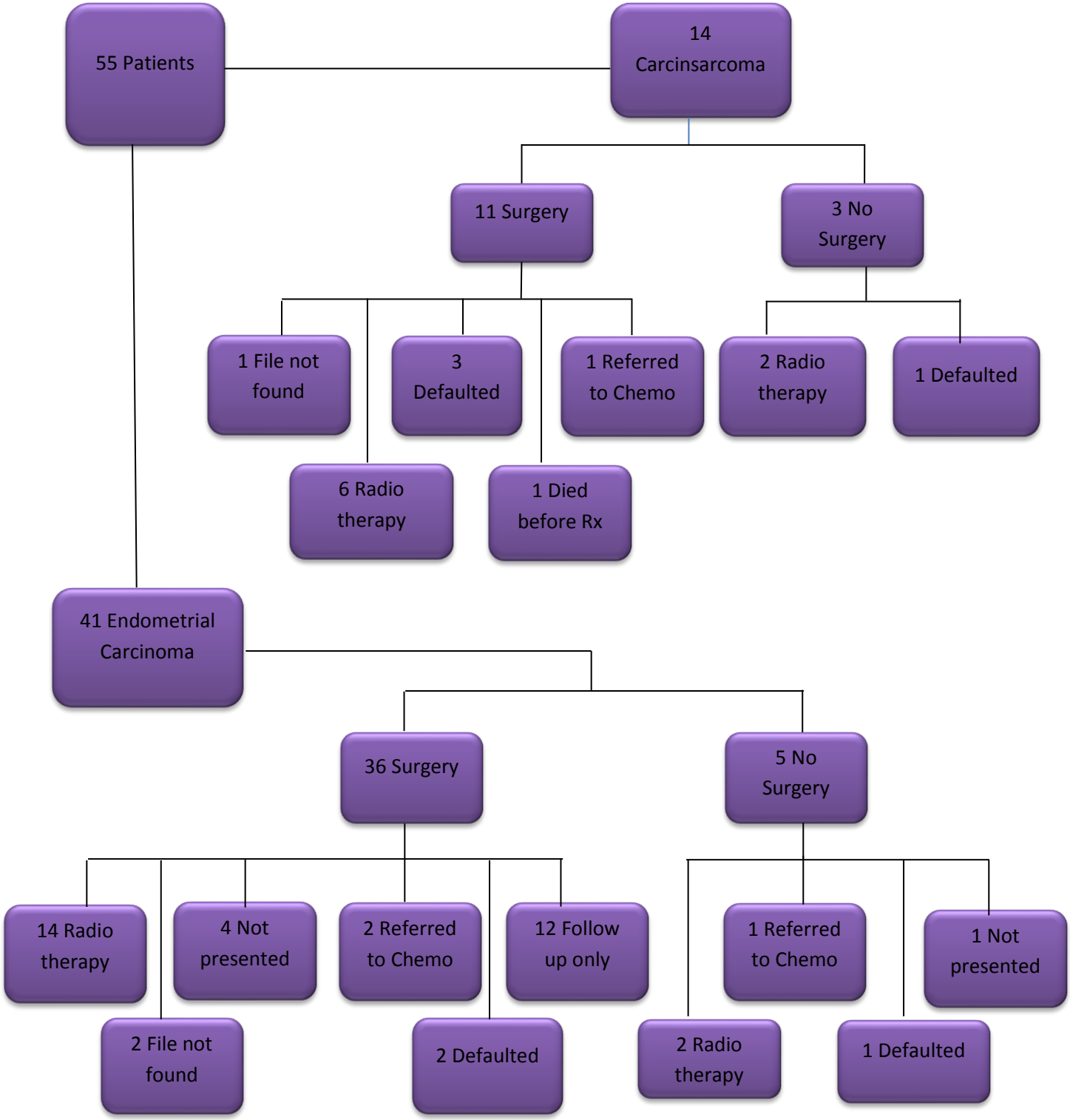


Figure 4.5 Flow diagram of management of patients

Of the 47 patients files available from CMJAH, four patients were referred to Chemotherapy, six patients defaulted prior to radiation therapy. There were 37 patients who continued treatment at the Radiation Oncology department and did not default. Twenty four of these patients received radiation therapy and 12 patients required only follow up after surgery. One patient died prior to radiation treatment. After one year 28 of the 37 patients (75.7%) were well with no signs of metastases, three patients (8.1%) had developed metastases (one to bone, one to brain and one to liver) and six patients (16.2%) had died within the year.

Of the six patients who defaulted radiation treatment, their outcome is unknown. Two of these patients had been stage 4 at diagnosis and could conceivably have also died prior to radiation treatment. The outcome of three of the patients referred to chemotherapy is unknown. One of these patient was well at eight months following chemotherapy. Seven patients who did not receive radiotherapy were well at one year follow up. The remaining five patients who did not continue their follow up for one year were contacted telephonically to ascertain their well-being.

		Type I (n=19)	Type II (n=22)	Carcinosarcoma (n=14)
Demographics (n=55)	Average Age	63.2	62.7	68.4
	Ethnicity: ○ Black ○ White ○ Coloured ○ Asian	 10 3 2 4	 17 2 2 1	 11 1 1 1
Stage at Presentation	Stage I	17	7	2
	Stage II	1	2	2
	Stage III	0	8	8
	Stage IV	1	5	2
Surgical Management (n=55)	Surgery	19	17	11
	No Surgery	0	5	3
Adjuvant Treatment (n=47)	Radiotherapy	5	12	8
	Chemotherapy	1	2	1
	No Adjuvant therapy: ○ Defaulted following surgery ○ Follow up only	 2 7	 1 5	 3 0
Outcome at 1 year (n=37)	Disease free	11	13	4
	Metastases	1	1	1
	Died	0	2	4

Table 4.3 Summary of patient demographics, management and outcomes one year after treatment

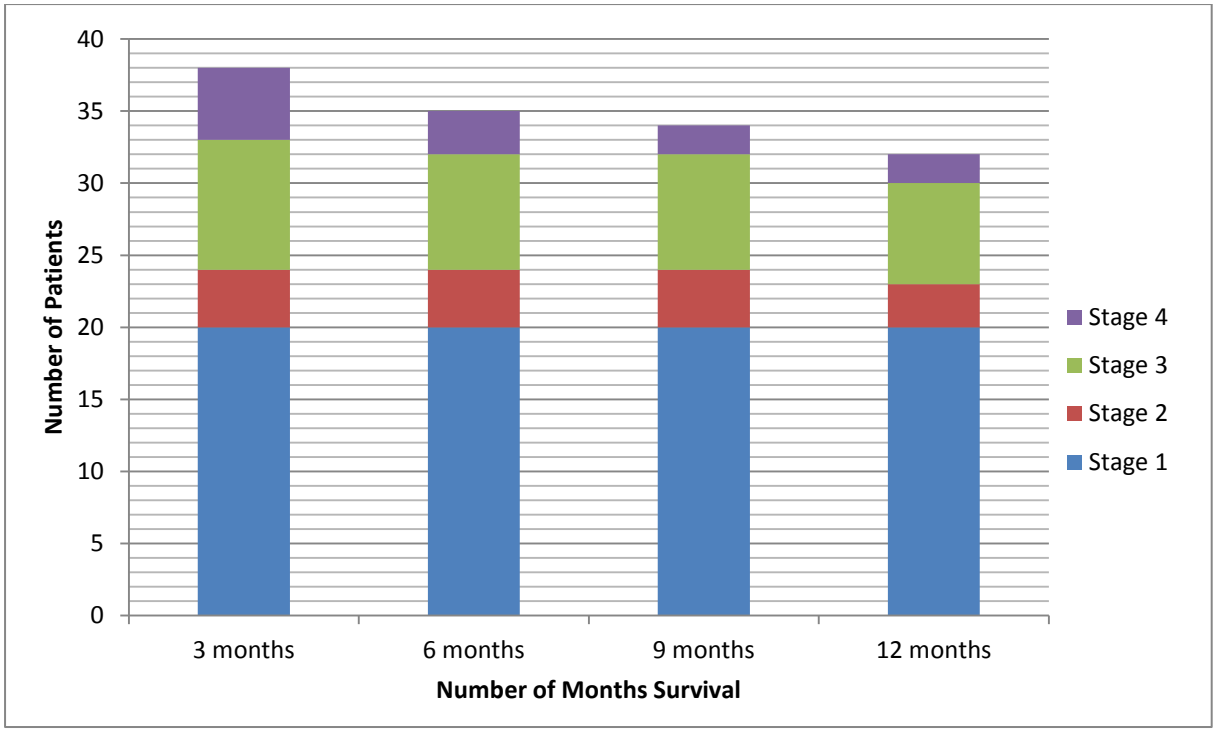


Figure 4.6 Number of months survival after commencement of radiation therapy

4.5.1 Outcome by stage

Of the six patients who died, one patient was diagnosed with stage 2, two were diagnosed with stage 3 and the three patients were stage 4 at diagnosis. All three patients who developed metastases were diagnosed with stage 1.

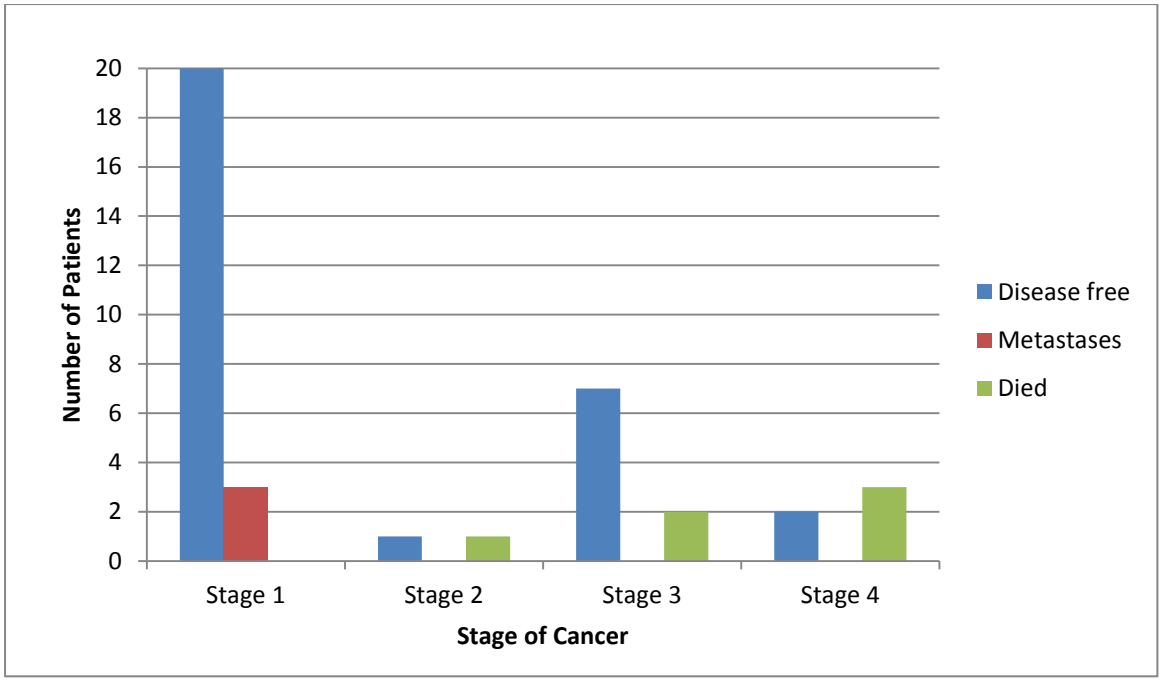


Figure 4.7 Outcome by stage one year after treatment

4.5.2 Outcome by histology

Of the patients with endometrial carcinoma (type I and II tumours), 24 patients were disease free after one year, two patients had died and two had developed metastases. Of the nine patients with carcinosarcoma who followed up at radiation oncology, four patients had died within one year of treatment, one patient developed metastases and four were disease free at one year.

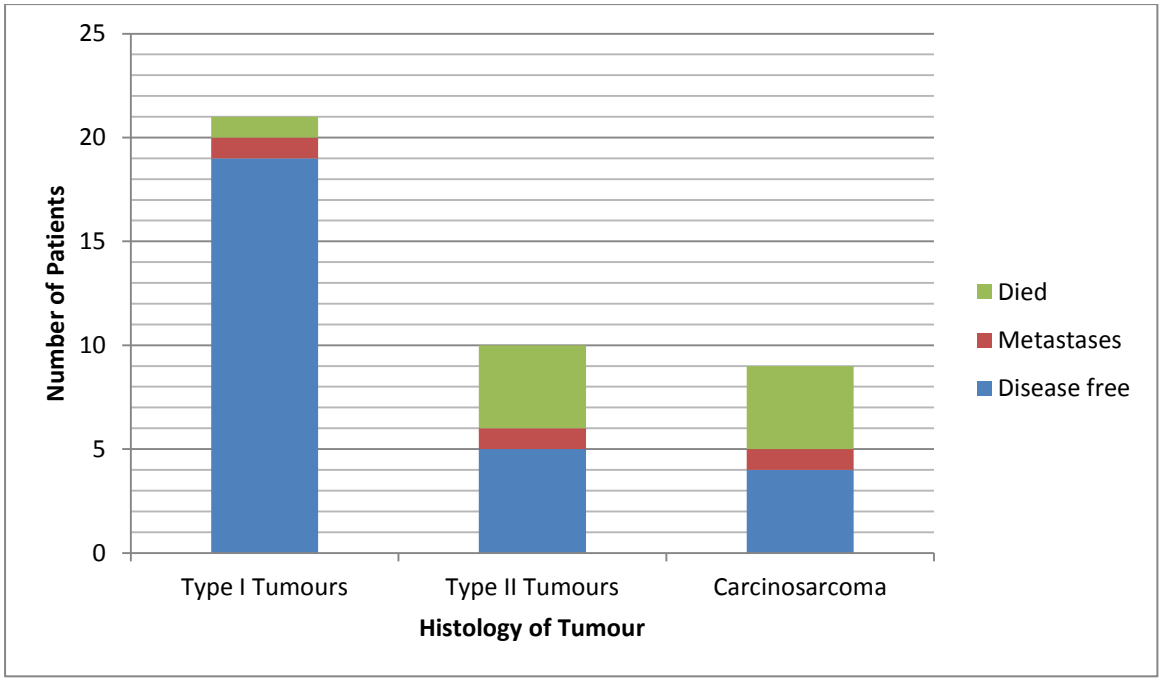


Figure 4.8 Outcome by histology one year after treatment

4.6. Waiting Times

4.6.1 Presenting Symptoms

The majority of patients (90.9%) presented with abnormal bleeding, either on its own or in conjunction with another symptom. 38.2% of the women complained of lower abdominal pain, 9.1% presented with a pelvic mass, 5.5% with per vaginal discharge and 14.5% of patients complained of other symptoms including hot flushes, dysuria, lower back pain and malaena. There was only one patient (1.8%) who was asymptomatic and was referred due to an abnormal pap smear result.

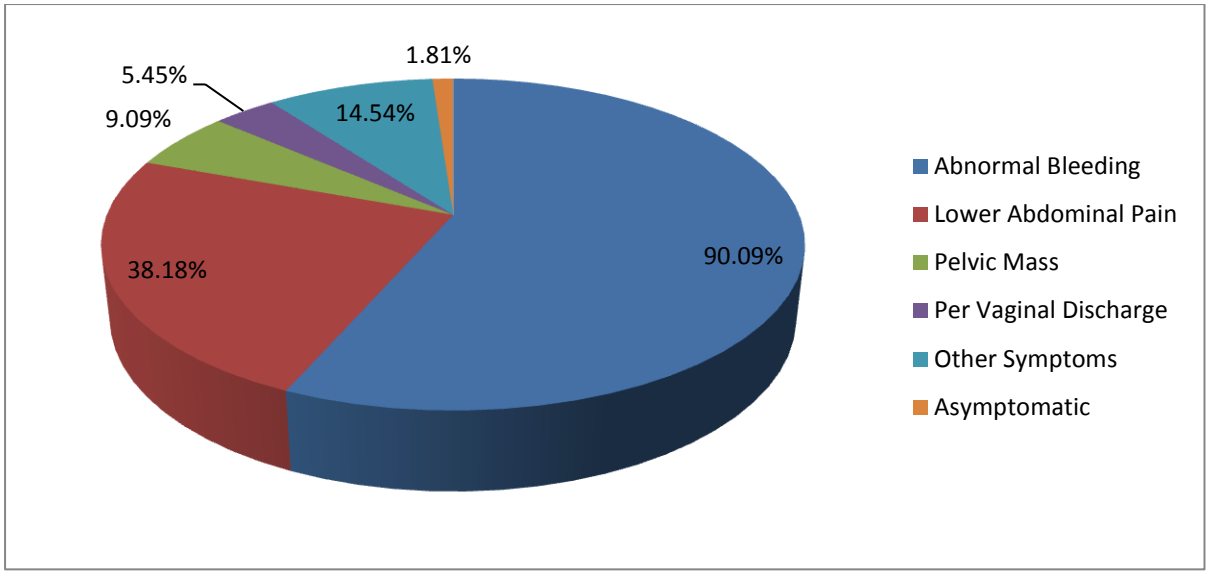


Figure 4.9 Presenting Symptoms

4.6.2 Initial Investigations to Definitive Management

There were 47 (85.5%) patients who underwent total abdominal hysterectomy and eight (14.5%) patients who did not have surgery. Of the eight patients who did not undergo surgery, six were then presented at CMJAH for radiation therapy, this being their definitive treatment. For the purpose of analysis of data they are still included in waiting time from investigation until definitive management. The mean number of days between a patient first presenting and being investigated for endometrial cancer at RMMCH until definitive management was 100.5 days, the median was 60 days and the range 6 - 832 days. Only 25.9% of patients waited 31 days or less for definitive management and 53.7% waited 62 days or less. The reasons for long waiting times were not apparent for the majority of patients. There were eight patients (14.8%) who waited more than six months (180 days) for definitive management. Of these eight patients, one defaulted the surgery appointment date and had to be rebooked, one patient required DD&C due to inadequate endometrial samples and in two patients the surgery was done for a benign indication and the cancer was an

incidental finding during histological examination. For four of these eight patients no reason for the extended delay was recorded.

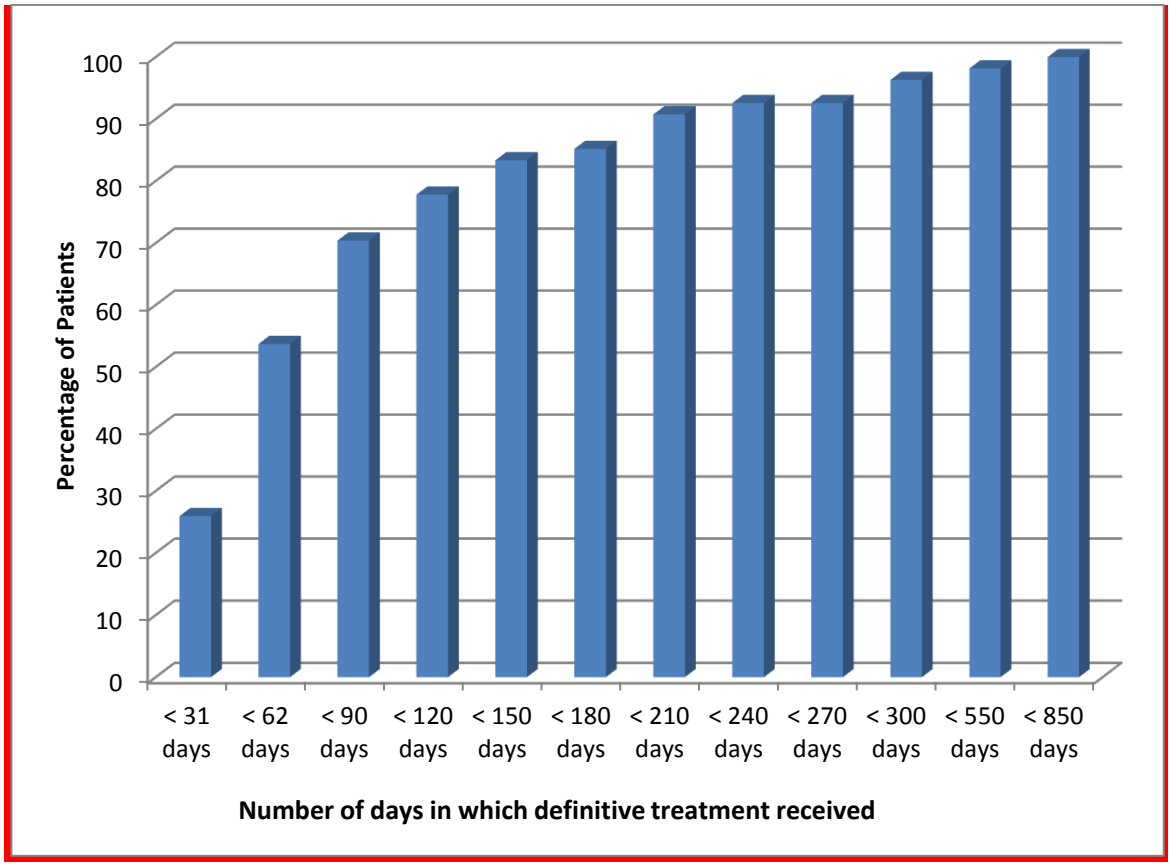


Figure 4.10 Cumulative numbers of patients receiving definitive treatment over time.

4.6.3 Patients requiring Diagnostic Dilation and Curettage

There were 39 patients (70.9%) who had an endometrial sample done on initial investigation. Of these, nine patients (23.1%) required repeat endometrial samples due to inadequate samples and seven of these nine patients required DD&C in theatre due to inadequate results following repeat endometrial sample. The delay from initial presentation of the patient until DD&C was done was variable. Five of the seven patients who required DD&C waited more than 60 days for the procedure from presentation.

4.6.4 Reasons for not having surgery

There were a total of eight patients (14.5%) who did not undergo Total Abdominal Hysterectomy. Of these patients three had been diagnosed with carcinosarcoma and five with endometrial carcinoma. The reasons for not undergoing surgery include advanced disease in five, poor medical condition in two and for unknown reasons in one patient.

4.6.5 Waiting time between Surgery and Adjuvant Treatment

There were 50 patients who were presented at the combined oncology meeting. Five patients were not presented following surgery, they either did not come for histology results or defaulted before presentation at CMJAH. The mean number of days from surgery to presentation was 51.2 days, the median 41 days and the range 3 - 266 days (0 - 38 weeks). 71% of patients were presented 52 days or less after surgery. The mean delay between presentation and treatment was 42.67 days and the median 40 days with a range 0 – 203 days.

CHAPTER 5: DISCUSSION

5.1 Study Objective 1: Stage of Disease

The majority of endometrial carcinoma is diagnosed in the early stages, with 85-90% of women in stage 1 or 2 (53). Our study differs from this as only 65.8% of our patients with endometrial carcinoma were in stage 1 or 2 at diagnosis. This percentage is still less than the 74.9% of patients in stage 1 at diagnosis in a multicentre study of 3434 patients by Brinton el al in the USA (7). This would indicate that our patients tend to present with later stage disease than those in developed countries. In terms of research from other African countries; Nyekyer in Ghana found 75% of patients in stage 1 or 2 at diagnosis and 59.9% were in stage 1 in a study by Missauoi et al in Tunisia (3, 60).

Carcinosarcoma is known to have a worse prognosis than endometrial carcinoma partly due to the higher percentage of women presenting with advanced disease (12). Carcinosarcoma has a high tendency for early extrauterine spread, about 60% of patients present with advanced disease extending beyond the uterus (52, 61). Bansal et al found that 41% of women with carcinosarcoma presented with stage 3 or 4 (13). In our study, 71.4% of women were stage 3 or 4 which is higher than that reported by both authors.

The reasons for the lower number of patients presenting in the early stages with both endometrial carcinoma and carcinosarcoma are most likely multifactorial. A review of patient staging according to race showed that 73% of white women will present with stage 1 compared to 54% of black women. Black women are more likely to present with stage 3 or 4 (27% vs 14% respectively) (36). Poor patient knowledge or poor understanding of the importance of certain symptoms most likely contributes to a delay in seeking medical attention. Abnormal uterine bleeding in pre or perimenopausal women may not be recognised as a symptom of underlying disease or may even be ignored due to the fear of being

diagnosed with cancer (59). Access to healthcare may be limited. South African hospitals deal with large numbers of patients, long waiting times to see specialists together with inefficient health systems may delay patient presentation and diagnosis. Also the population in question is older and elderly women may not be able to get to a health facility by themselves due to either physical or monetary reasons and may have to rely on family or friends for help (62).

5.2 Study Objective 2: Proportion of Histological Types

Low grade endometrioid adenocarcinoma is usually the most common histological type of endometrial cancer (7). A study by Brinton et al found 65.4% of patients had low grade adenocarcinoma. This was by far the highest proportion followed by high grade adenocarcinoma with 10.3%, papillary serous carcinoma with 9.5% and clear cell carcinoma with 2.2%. They found 4.1% carcinosarcoma, 1.2% with mixed histology and 7.3% with unspecified endometrial carcinoma (7). These findings are very different to our study findings. We found low grade adenocarcinoma was almost half of the expected at 34.5%. The percentage of carcinosarcoma and high grade adenocarcinoma are both higher (25.5% vs 4.1% and 23.6% vs 10.3% respectively). The number of papillary serous tumours was also higher in our study (12.7% vs 9.4%) and the only group of tumours that was similar between the two studies was clear cell carcinoma (1.8% vs 2.2%).

The differences may be explained by the ethnic composition of the women in question. In our study 78.2% of the patients were black or coloured and 39.5% of these patients had a type II tumour or carcinosarcoma. Many studies have shown previously that white women tend to develop endometrioid adenocarcinomas and that black women tend to develop high grade adenocarcinoma, type 2 tumours and carcinosarcoma (36, 52).

5.3 Study Objective 3: Risk Factors

5.3.1 Menarche

Early menarche is associated with an increased risk of developing endometrial cancer. Brinton et al found a 2.4 times increased risk for patients with menarche at less than 12 years (7). In our study more than 50% of patients were more than or equal to the age of 15 years and less than 15% were 12 years or less.

5.3.2 Menopause

Late menopause after 55 years has been associated with increased risk due to increased cell turnover of the endometrial lining. This increased risk in most likely multifactorial and results due to late menopause combined with early menarche and nulliparity (2). In our study the median age of patients was 52 years and only 15.4% of patients were more than 55 years when experiencing menopause.

5.3.3 Parity

There is a two to three fold increased risk of endometrial cancer in nulliparous patients, increased numbers of ovulatory cycles result in higher oestrogen exposure for longer periods of time. Multiparity decreases the risk of endometrial cancer by up to 70% (26). In our study, 73.2% of patients with endometrial carcinoma were multiparous indicating multiparity is not protective in our population. This is similar to the finding by Nyekyer in Ghana where almost 50% of patient had a parity or five or greater (3). A possible explanation for this may be that South African women give birth and complete their families at younger ages. This is

supported by the fact that 65.8% of women giving birth in South Africa 2014 were between the ages 15 and 29 years (63).

Secondly, obesity is a recognised risk factor in the development of endometrial cancer (7, 17). With the high percentage of overweight and obese South African women overall, about 55.4% of women between 25 and 34 years are overweight or obese (18). These high levels of malnutrition increase the risk of excessive weight gain during pregnancy and retention of weight post pregnancy (64). Thus the protective effect of increased parity may be negated by obesity. This study is under-powered to explore this theory.

5.3.4 Gravidity

More than 75% of patients with both endometrial carcinoma and carcinosarcoma had had two or more pregnancies. There was a positive association between gravidity and histological grade ($p=0.04$) but not stage of cancer ($p=0.38$).

5.3.5 Patient weight

Increasing BMI has a Relative Risk of 1.59 to 2.89 (CI 95%, 1.50-1.68 and 2.62-3.18) of developing endometrial carcinoma (2). There were only 16 patients in our study where BMI calculation was possible. This is not a sufficient number of results to comment on however 62.5% of these patients had a BMI greater than 30.

5.3.6 HRT

Hormone replacement therapy, namely unopposed oestrogen therapy has been shown to increase the risk of adenomatous hyperplasia five times (26). In this study there was only one patient who had previously taken any kind of hormone replacement.

5.3.7 Tamoxifen

Tamoxifen has been shown to increase the risk of endometrial cancer in women (28), however only one patient in our study had a history of prior tamoxifen use.

5.3.8 Hormonal Contraceptives

Contraceptive use has been shown to be protective in terms of developing endometrial cancer (27). In our study, only 20.0% of patients had a previous history of taking hormonal contraceptives.

5.3.9 Smoking

Smoking is usually associated with a decreased risk of endometrial cancer as tobacco has an antioestrogenic effect (2). In our study there were only five patients who had ever smoked and there was no association between smoking and histology ($p=0.78$).

5.3.10 Previous History of cancer

Previous history of breast cancer is associated with an increased risk of endometrial cancer. In our study there was a positive association found between previous history of cancer and stage of cancer (p=0.012). However, considering there was only one patient with a previous history of breast cancer meaningful inferences cannot be made.

5.3.11 Radiation therapy

Radiation shown to be associated with increased risk of type 2 tumours and carcinosarcoma (34), however no patients in our study had had previous radiation therapy.

5.4 Study Objective 4: Demographic Factors

5.4.1 Age

A review by Dinkelspiel et al reported a median age of 61 years at diagnosis for endometrial carcinoma which is comparable to our study which showed a median of 63 years (2). We found that 87.8% of the patients were above or equal to 55 years. This figure is similar to those of the South African National Cancer Registry 2009 where 81.5% of women with uterine cancer were more than 55 years of age (5).

A Nigerian study showed a mean age of 62.4 years (4) which is equal to our result of 62.97 years. However the results differed greatly from those of Nyekyer in Ghana who found a mean age of 56 years with only 72.9% of patients being over the age of 50 years (3).

The mean age of our patients with carcinosarcoma was 68.4 years with the youngest patient being 52 years old. This finding is in keeping with other work by Felix et al demonstrating a mean age at diagnosis of 67 years for women with carcinosarcoma (17).

5.4.2 Race

According to the South African National Cancer Registry 2009, the total number of women diagnosed with uterine cancer was 1073. Of this 62.3% were black and 17.8% were white (5). Our study population had a higher percentage of black women (69.1%) and a lower percentage of white women (10.9%). These figures are most likely due to the composition of the population that RMMCH Hospital manages. The hospital serves a much larger proportion of black than white patients from the surrounding areas. A much larger proportion of white than black patients who live in the catchment area can afford to be treated at private hospitals. There were 9.1% coloured patients and 10.9% Asian patients which are also quite different to the South African statistics of 12.6% and 6.4% respectively. Once again this difference is most likely due to the population living in the catchment area of RMMCH.

In the United States there is a higher rate of uterine cancer in white women than black women. The study done by Oliver et al in military personnel in the US showed 2057 white women had been diagnosed with endometrial cancer compared with only 183 black women (40). Similarly, a review of the SEER database by Wright et al over a 16 year time period reported close to 70 000 white women with endometrial cancer compared to roughly 5500 black women (35).

5.5 Study Objective 5: Treatment Received and Outcomes

5.5.1 Treatment Received

All of the 47 patients who underwent surgery had a simple Total Abdominal Hysterectomy and Bilateral Salpingooophorectomy. None of the patients had lymphadenectomy done. The inclusion of lymphadenectomy is controversial but has been found to improve the five year survival in patients with high risk tumours and stage 2 to 4 disease (16). Therefore it would have been beneficial for 37 patients (78.7%) to have had lymphadenectomy at the time of surgery. The patients with stage 1 disease would not be as detrimentally affected considering the evidence from the ASTEC trial which showed lymphadenectomy in stage 1 having only morbidity and no survival advantage associated with it (19).

Without having had lymphadenectomy done, the patient staging is less accurate leading to possible over or under treatment with adjuvant radiotherapy. The inaccuracy of staging may negatively impact the validity of the prognosis and the appropriate counselling of the patient.

The omission of the lymphadenectomy is not in keeping with the protocol for treatment of endometrial cancer at the University of Witwatersrand. RMMCH is a hospital affiliated with the University but it does not have a Gynaecology oncology unit. It is possible that the lymphadenectomy was not done due to a lack of expertise in this area. The increased operating time required would also limit the theatre time for other patients therefore increasing waiting times for elective procedures at an already busy government hospital. Lastly, for some women the finding of endometrial cancer may have been incidental on histological examination postoperatively therefore the opportunity for lymphadenectomy was missed. However, referral of all oncology patients to CMJAH for surgery is not feasible as it would place an even greater burden on the Gynaecology oncology unit at CMJAH**.**

Radiotherapy is given by the CMJAH Radiation Oncology department according to the current literature. Stage 1 with low risk tumours do not receive radiotherapy but are followed up only. Patients with stage 1B, high risk tumours are given radiotherapy together with stage 2, 3 and 4 patients. The majority of patients in this study were managed in this way. However, there are a few inconsistencies. There were four patients with Stage 1 A or B, low risk, who were given radiotherapy and one patient Stage 1 B, high risk, who did not receive radiotherapy but was followed up. There were three patients with low risk tumours in Stage 1 who were not presented at the combined oncology meeting. Although these patients did not qualify for adjuvant treatment it would have been preferable for them to be follow up at the oncology department.

Four patients were referred for chemotherapy. They comprised a mixture of type I, type II and carcinosarcoma tumours in stage 3 and 4. This is in keeping with the literature where chemotherapy may be used for treatment of advanced stage endometrial cancer or carcinosarcoma. It is, however, unclear as to why only these specific patients were referred for chemotherapy while the majority of patients received the standard radiotherapy as per the department protocol (46).

5.5.2 Outcomes

Our study showed a disease free survival of 75.6% and an overall survival of 83.7% one year after radiation therapy was completed. These figures include the patients that were only followed up and did not receive radiation therapy. They are well below the estimated overall survival of patients in developed countries. In these countries overall survival is 92% at one year and 82% at five years. Our results at one year are more in keeping with those at five years in a developed country. In our study roughly 25% of patients had carcinosarcoma and

almost 45% of patients were stage 3 or 4 at diagnosis. These factors most likely account for the lower overall survival as stage at presentation is one of the most important prognostic factors in both endometrial carcinoma and carcinosarcoma (2, 12). As over 69% of the patients in our study were black, these results are in keeping with the findings of many other studies that black women have a poorer prognosis when diagnosed with endometrial cancer (25, 36).

There is very little data available from African studies as to the survival of women with endometrial cancer. This is most likely due to poor follow up and the fact that facilities for surgery and adjuvant treatment are severely lacking. For example, in Ghana, only 37.5% of patients diagnosed with cervical cancer could be treated. As with our study, many patients in Ghana with endometrial cancer present in advanced stages of disease (3).

5.6 Study Objective 6: Compare Endometrial Carcinoma and Carcinosarcoma

5.6.1 Stage at Presentation

More than 65% of patients with endometrial carcinoma presented with early stage disease (stage 1 or 2) compared with carcinosarcoma where over 70% of patients presented with stage 3 or 4. This is in keeping with other studies which have shown carcinosarcoma to be a more aggressive tumour which spreads beyond the uterus more quickly resulting in more than half of patients with stage 3 or 4 at time of diagnosis (52, 61).

5.6.2 Risk Factors

5.6.2.1 Menarche

Early menarche, less than 12 year of age, is associated with increased risk of type I tumours (7, 17). In our study, more than 50% of patients with both endometrial cancer and carcinosarcoma were more than or equal to 15 years at menarche. There was no association between age at menarche and histology (p=0.32).

5.6.2.2 Menopause

Carcinosarcoma predominantly occurs in postmenopausal women (52), this is supported by our study where no women with carcinosarcoma were premenopausal compared with five premenopausal women in the endometrial carcinoma group. However, neither menopausal status nor age at menopause were significantly associated with histology (p=0.59 and p=0.72 respectively).

5.6.2.3 Parity

For endometrial carcinoma multiparity is protective whereas for carcinosarcoma multiparity is a risk factor (7, 26). In our study, there was a high percentage of multiparous patients with endometrial carcinoma not in keeping with the literature. 85.6% of patient with carcinosarcoma were multiparous, however, statistically parity was not significant in terms of histological type (p=0.18).

5.6.2.4 Gravidity

In the literature gravidity is not listed as a protective factor. It cannot be equated to parity as not all pregnancies result in a viable baby however a pregnancy will disrupt the normal cycle

for a period of time preventing continuous ovulation (26). There was an association found between gravidity and histological type (p=0.04).

5.6.2.5 Patient weight

Obesity is a risk factor for type I tumour due to increase in oestrogen production (7, 17). Carcinosarcoma is also known to be associated with obesity (11). In our study the mean patient weight was 81.5 kilograms and 62.5% of patients had a BMI greater than 30kg/m^2 indicating that the majority of our patients were overweight/ obese. There was no association between patient weight and histology (p=0.86).

5.6.2.6 Hormone Replacement Therapy

HRT is a risk factor in type I tumour due to unopposed oestrogen production (7, 17). There was no association between HRT and histology (p=0.22).

5.6.2.7 Tamoxifen

Tamoxifen has been associated with increased endometrial tumours particularly carcinosarcoma (8, 33), however our in our study tamoxifen was not significant in terms of histology result (p=0.07).

5.6.2.8 Hormonal Contraceptives

Hormonal contraceptive use is protective in terms of developing endometrial cancer (25, 26). There was a low rate of contraceptive use (20.0%) in our study population. There was no association between hormonal contraceptives and histology (p=0.20).

5.6.2.9 Smoking

Smoking is generally protective for developing type I tumours but a risk factor for type II tumours and carcinosarcoma (2). There was no association between smoking and histology (p=0.78).

5.6.2.10 Previous History of cancer

Patients with a previous history of breast cancer have a higher risk of endometrial cancer (2). Patients with type II tumours are more likely to have a history of breast cancer with tamoxifen use. Whereas type I, grade 3 tumours are associated with breast cancer without tamoxifen treatment. Indicating that tamoxifen is the more important factor in type of tumour development (7). In our study there was no association between previous history of cancer and histology (p=0.22).

5.6.2.11 Radiation therapy

Radiation therapy has been associated with a higher incidence of type II tumours and carcinosarcoma (34), however in our study there were no patients with previous radiation therapy.

5.6.3 Demographics

5.6.3.1 Age

Patients with endometrial carcinoma were found to be younger than those with carcinosarcoma, with mean ages of 62.9 and 68.5 years respectively. This is in keeping with studies showing patients with carcinosarcoma tend to be older (17). The endometrial carcinoma group also proved to have a much wider range of ages at diagnosis, with patients ranging from 36 to 85 years of age compared to the patients with carcinosarcoma who were all over the age of 52 years at diagnosis.

5.6.3.2 Race

The majority of the patients in our study were black (69.1%). Of the white patients in the study group, 83.3% had endometrial carcinoma and 16.6% had carcinosarcoma, compared with 71.1% of black patients with endometrial cancer and 28.9% with carcinosarcoma. These findings are similar to studies from America where carcinosarcoma is more common in black women, most likely due to an underlying biological difference (36).

5.6.4 Patient Characteristics

5.6.4.1 Co-morbidities

The percentage of patients with hypertension was similar in both the patients with endometrial carcinoma and those with carcinosarcoma (70.7% vs 78.5%). According to the South African Demographic and Health Survey of 1998 the overall prevalence of hypertension in South Africans was 55% (65) which is lower than the percentage in our

study. As our study predominantly comprises older women, this difference is to be expected. There were more patients with carcinosarcoma who had diabetes than the patients with endometrial cancer (21.4% vs 12.2%). There was a poorer overall survival for patients with carcinosarcoma, however, it is difficult to say whether this is as a result of the more aggressive histology or due to the higher rate of diabetes which has been shown to be associated with poorer overall survival in women with endometrial cancer (42). The number of patients with other medical illness was also similar between the two groups (21.9% vs 21.4%).

There were only two patients with three or more medical conditions and a total of three patients who did not undergo surgery due to medical conditions. This would indicate that despite the fact that roughly 75% of patients had at least one or more medical condition, there were only 5.5% who were not fit for surgery.

5.6.4.2 HIV

The rate of HIV was similar between both groups of women, with 7.6% of women with endometrial carcinoma and 7.1% of women with carcinosarcoma. This is to be expected considering the fact that cancer of the uterus is not an HIV and AIDS related malignancy. This percentage of women with HIV is well below the estimated prevalence of HIV in adults aged 15 to 49 years of 17.9% (43), but similar to the estimated prevalence of 7.1% for women older than 50 years (66).

The positive retroviral status of the four patients with HIV does not appear to have any effect on the stage of disease at presentation. Half of the patients had early stage disease and the other half had late stage disease at diagnosis. HIV status or antiretroviral use does not appear

to contribute to progress of the endometrial cancer as previously suggested by case studies (44).

5.6.5 Outcomes

When considering the overall of survival of patients according to histology, there was an overall survival of 85.7% for patients with endometrial carcinoma compared to 44.5% for those with carcinosarcoma. This result is to be expected considering the aggressive nature of carcinosarcoma (61) and the late stage of presentation of most of our patients with carcinosarcoma (71.42% stage 3 and 4).

5.7 Study Objective 7: Waiting Times

5.7.1 Presenting symptoms

A review by Dinkelspiel estimates more than 95% patients will present with symptoms of endometrial cancer (2). This is in keeping with our study where only 1.8% of our patients were asymptomatic. Abnormal uterine bleeding is the most common symptom and may be present in anywhere from 69% to 90% of patients (54, 55, 56). This again is in keeping with the findings of our study of 90.9% of patients with abnormal bleeding.

5.7.2 Initial Investigation to definitive management

The United Kingdom national cancer target for treatment is definitive treatment within 62 days. An observational study by Johnson et al with 142 endometrial cancer cases in South

West England showed that 82% of patients were treated within the target and only 18% waited longer than 62 days from GP referral to definitive management. However, only 25% of these patients received treatment within 31 days (67).

The Ministry of Health in New Zealand has adopted similar guidelines with a target of 62 days from referral to definitive treatment (55). The results of a retrospective study by Kang et al of patients referred to Dunedin Hospital in New Zealand, showed 20% of patients had been treated within the guideline time period of 62 days and the median number of days from referral to treatment was 93 days (55).

In our study 26.4% of patients received definitive treatment within 31 days which is comparable to the UK study findings but in contrast we found that only 52.8% of our patients were treated within 62 days. Over 77% of our patients were treated within 120 days. Compared to results of the New Zealand study we appear to be doing well. As the percentage of patients treated within 62 days is higher and the median number of days from our study was 60, lower than that of the New Zealand study.

One of the authors' reasons for such poor figures in the New Zealand study was that patients often did not attend follow up appointments or did not agree with or understand the treatment course and so were not willing to follow the programme (55). These are most likely important factors in our study and our population considering the fact that two patients missed their surgery appointments and had to be rebooked and ten patients did not attend follow up appointments and further treatment following surgery.

It is important to consider when comparing the above that the time frames include a referral period and waiting time to see a specialist, whereas the time interval in our study is from the first consultation at the hospital. This may mean that the results are not comparable. But when we consider that roughly 35% of our patients are seen as self-referrals and there is

usually a negligible waiting time as patients do not have to wait for an appointment. The referral time for our patients is more dependent on patient factors such as transport, money and arranging time off work.

In our study, 15.1% of patients had their surgery more than 6 months after being investigated. However, in two of these patients the cancer was an incidental finding on histology report post operatively and the patients were initially booked for hysterectomy for benign reasons. If these two patients are excluded then only 11.7% of patients were delayed for more than six months. These figures are not a good reflection on the general waiting times for patients requiring elective surgery at RMMCH.

Reasons given by Kang et al for delays in patient care include multiple patient co morbidities and shortages in theatre time (55). In our study, the presence of co morbidities does not seem to have a large influence as less than 10% of our patients had three or more medical conditions. However, shortage of theatre time most likely plays a large role in the delay of patient management.

5.7.3 Diagnostic dilation and curettage

In our study DD&C was required for seven out of 39 patients (17.9%) who had an inadequate result on endometrial sampling compared to 30% of patients in the study done in New Zealand by Kang et al. In their study, almost a third of patients required DD&C in theatre due to inadequate or unsuccessful endometrial sampling (55).

The patients in our study requiring DD&C had a mean waiting time of 92.7 days for theatre time. However, of the 11 patients who waited more than four months for surgery

(Hysterectomy), only two of them underwent DD&C beforehand to establish cancer diagnosis. Therefore DD&C was not a prominent cause of delay in surgery in our study.

In contrast, Kang et al found the delay due to patients having to undergo DD&C was very lengthy and concluded that office hysteroscopy and endometrial sampling was preferable to having to wait for theatre time. They also cited poor patient adherence as one of the causes of treatment delays (55).

5.7.4 Patients not undergoing surgery

In our study eight patients did not undergo surgery. Six of these patients were stage 4 and were thought to be inoperable. There were, however, three other patients with stage 4 who underwent surgery. It is most likely that for these three patients the extent of their disease was not known as no imaging had been done prior to surgery. The percentage of patients presenting with stage 4 in our study is similar to that of the study done by Nkyekyer in Ghana (16.4% vs 18.9%). There is no mention in the report by Nkyekyer as to how many of the patients with advanced disease were inoperable (3).

5.7.5 Waiting time between Surgery and Adjuvant Treatment

The time interval between surgery and presentation at the combined oncology meeting is usually dependant on the length of time taken for the histology report to be ready. The standard follow up interval given at RMMCH is six weeks or 42 days in which time it is expected that histology results will be available. In our study the mean number of days from surgery to presentation is 51.2 days with a range of one to 38 weeks.

However when adding the median number of 40 days from presentation to radiation treatment, the total of 82 days from surgery to radiation treatment is well above the median of 48 days and range of four to eight weeks found by Sorbe et al in their study of treatment delays in Denmark (12).

5.8 Limitations

The main limitation is that this is a retrospective study where not all patient files were available and where data sets had varying degrees of missing data. Due to the limited time period of four years, the sample size is small and due to the uncommon nature of carcinosarcoma the numbers of patients in each group are unequal which may affect the comparison of endometrial carcinoma and carcinosarcoma. There is a high rate of loss to follow up in terms of treatment. This will bias the results of outcome. Lastly, endometrial carcinoma is a disease of women mostly in their 6^{th} and 7^{th} decades. This may result in recall bias as the information provided by patients, for example age at menarche and menopause, contraceptive use, may not be completely accurate resulting in an information bias.

5.9 Recommendations

We have identified that there are long delays in patient care, greatly in excess of the recommended waiting times in both the United Kingdom and New Zealand. Delays are predominantly related to delays in undergoing surgery. In order to reduce these waiting times, patients diagnosed with cancer on initial investigations need to be prioritised on theatre lists or booked on dedicated oncology theatre lists. Another area for improvement involves the processing of pathology specimens. These specimens need to be marked urgent or the

pathologist involved with the specimen needs to be contacted in order to ‘fast track’ the analysis.

Patients are generally given a follow up date of six weeks on discharge from hospital after surgery. It may be preferable to contact patients telephonically as soon as the histology result is ready in order to facilitate quicker presentation to oncology department for adjuvant treatment. It might be advisable to develop a separate out-patient clinic at RMMCH for cancer patients to follow up at to ensure that appointments are available and clinic waiting times are shorter. Patients with early stage disease requiring only follow up can also be seen after presentation and discharge from CMJAH Oncology clinic. This may also be an environment where extra time can be taken to counsel patients about their condition and treatment options. This may be helpful in improving patient adherence to treatment and follow up.

CHAPTER 6: CONCLUSION

It is clear from our study that our patients presented with more advanced disease than women in developed countries. This is most likely as a result of poor patient knowledge, limited access to health services as well as fear of the diagnosis. Most findings regarding demographics were similar to the existing body of literature. However, in our study a larger proportion of women had more aggressive tumours. These factors contributed to a lower than expected overall survival at one year. The study has shown that intervals between presentation and treatment are particularly long due to high patient loads in Government hospitals. This indicates a need to improve waiting times and patient care. Better education of patients as to the importance of postmenopausal bleeding and of adherence to treatment is required in order to improve patient follow up and long term outcomes.

CHAPTER 7: FUNDING

This study had no direct costs associated with it besides printing and this was borne by the researcher.

CHAPTER 8: APPENDIX

8.1 Data Sheet

Data Collection Sheet							
Research No.							
Demographics							
Age		_____					
Ethnicity		1. African/ 2.Asian/ 3.Coloured/ 4.Indian/ 5.White/ 6.Unknown					
Weight		_____					
Height		_____		BMI	_____		
Gynae History							
Menarche	_____						
Parity	_____	Gravidity	_____				
Contraceptive use		1.Yes/ 2.No/ 3.Unknown					
Type of contraceptives used		1.Oral/ 2.Injectable/ 3.IUCD					
Number of years contraceptives used			_____				
LMP		_____	Menopausal status		1. Pre/ 2.Postmenopausal		
Age at Menopause		_____					
Medical history							
Diabetes		1.Yes/ 2.No/ 3.Unknown					
Type		1.Type I/ 2.Type II		Number years on treatment			_____
Hypertension		1.Yes/ 2.No/ 3.Unknown		Number of years on treatment			_____
Previous history Cancer		1.Yes/ 2.No/ 3.Unknown					
If Yes, What kind of cancer		_____? Unknown					
Treatment given		1.Radiation/ 2.Tamoxifen/ 3.Other/ 4.Unknown					
Medications							
HRT		1.Yes/ 2.No/ 3.Unknown					
What treatment given		_____/ Unknown					
Duration of treatment		_____/ Unknown					
Other chronic medications		1.Yes/ 2.No/ 3.Unknown		Which medication		_____	
Social							
Smoking		1.Yes/ 2.No/ 3.Unknown					
Pack Years		_____					
Presentation							
Presenting symptoms		1.PVB/ 2.LAP/ 3. Mass/ 4. PV Discharge/ 5. Other/ 6.None/ 7.Metasteses/ 8.Unknown					
Other symptoms?		_____					
Referral Facility		1. Local clinic/ 2. Primary or secondary level Hospital/ 3. Private GP or specialist/ 4.Self					
		5. HJH/ 6.Unknown					
Investigations							
Initial investigations done		1.Papsmear/ 2.Z-sample/ 3.ultrasound/ 4.CT scan/ 5.CXR/ 6.Other					
For papsmear/ Z-sample: were the samples adequate?				1.Yes/ 2.No			
If No: which test was inadequate		1.Papsmear/ 2.Z-sample					
Was the test repeated		1.Yes/ 2.No		How many times_____			
Results of investigations							
Papsmear		1.Normal/ 2.LGSIL/ 3.HGSIL/ 4.ASCUS/ 5.Ca/ 6.Other/ 7.Unknown					
Z-Sample		1.Normal/ 2.Endometrioid/ 3.MMMT/ 4.Other					
Results of other investigations		_____					
HIV Status		1.Non Reactive/ 2.Reactive/ 3.Unknown					
If Reactive, On HAART		1.Yes/ 2.No/ 3.Unknown					
When was HAART started		_____/ Unknown					
CD4 count		_____/ Unknown					

Histology Result	1.LG Adenoca/ 2.HG Adenoca/ 3.Papillary serous/ 4.Clear cell/ 5.Poorly differentiated/
	6.Carcinosarcoma/7. Other
Staging	1.Stage I/ 2.Stage II/ 3.Stage III/ 4.Stage IV
Evidence of metastesis on Abd US	1.Kidney/ 2.Liver/ 3.Other/ 4.US not done/ 5.Unknown
Evidence of metastesis on CXR	1.Yes/ 2.No/ 3.CXR not done/ 4.Unknown
Staging from histology report	_____
Other imaging done	_____
Evidence of local metastesis	1.Yes/ 2.No
Evidence of other metastesis	1.Yes/ 2.No
If Yes, Where	
Treatment decision	1.Chemo/ 2.DXT/ 3.Other/ 4.None
	1.Curative/ 2.Palliative
Treatment received	_____
Outcome at 1 year	1. Deceased/ 2.Living with disease/ 3.Living disease free/ 4.Recurrence/ 5.Metastesis
	6.Unknown (lost to follow up)
Timeline	
Date of initial presentation and	_____
investigation	
Date of surgery	_____
Date of presentation at Oncology	_____
meeting	
Date treatment 1st received	_____

8.2 Ethics Certificate

R14/49 Dr Susan Branch

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130861

NAME: (Principal Investigator)	Dr Susan Branch
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Retrospective Record Review of Patients Diagnosed with Endometrial Cancer and Carcinosarcoma at Rahima Moosa Mother and Child Hospital receiving Treatment at Charlote Maxeke Johannesburg Academic Hospital (Changed title 08/08/2014)
DATE CONSIDERED:	30/08/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Norma Pirani
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/08/2013

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

DECLARATION OF INVESTIGATORS

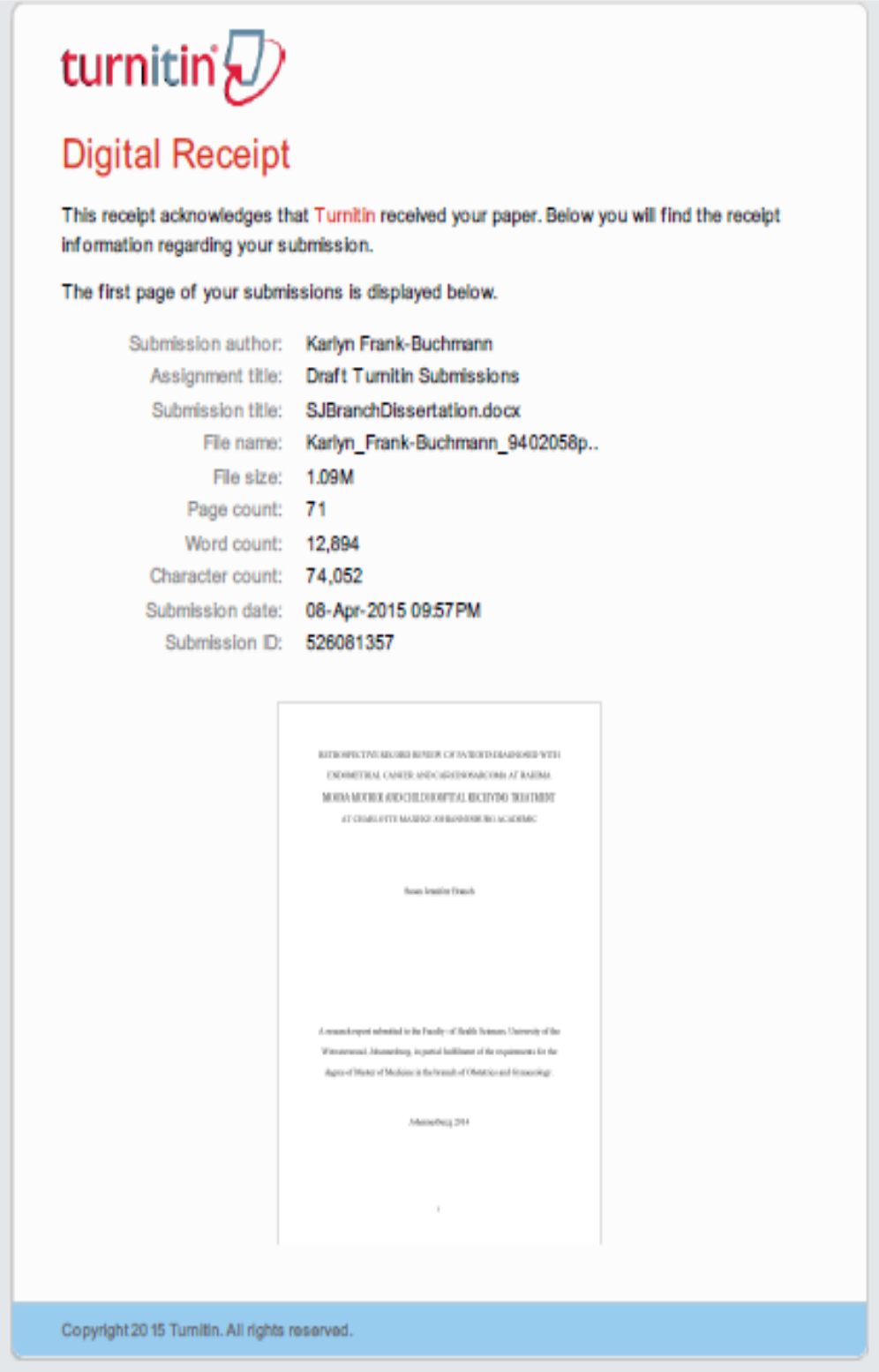
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I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

8.3 Turn-it-in Report

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CHAPTER 9: REFERENCES

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