GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF RADIOLOGY/ ONCOLOGY & RADIOTHERAPY

ENDOMETRIAL CANCER – A 10-YEAR REVIEW OF CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOME

DISSERTATION SUBMITTED TO THE FACULTY OF RADIOLOGY AND ONCOLOGY& RADIOTHERAPY IN PARTIAL FULFILMENT OF REQUIREMENT FOR THE CONFERMENT OF A FELLOW OF THE GHANA COLLEGE OF PHYSICIANS (FGCP)

DR MARY – ANN DADZIE

MBChB (2007), MGCP (2016)

NATIONAL RADIOTHERAPY ONCOLOGY AND NUCLEAR MEDICINE CENTER

KORLE BU TEACHING HOSPITAL

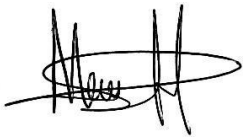
MARCH 2022

DECLARATION

I, Mary – Ann Dadzie declare that ‘‘I have wholly undertaken this thesis therein under supervision and that except portions where references have been duly cited, this thesis proposal is the outcome of my research.’’

March, 2022

Mary – Ann Dadzie



……

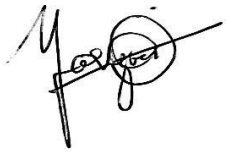
CERTIFICATION

This is to certify that this research work on" Endometrial cancer – A 10- year review of clinicopathological features and treatment outcome" was written by

Mary – Ann Dadzie.

I have examined and endorsed it for acceptability by the Ghana College of Physicians and Surgeons.

Dr Joel Yarney



……..……

ACKNOWLEDGEMENT

I am exceedingly grateful to The Lord Almighty for the special grace to complete this dissertation to His glory. I could never have succeeded without His continuous and never-ending love, guidance and enabling grace.

I wish to acknowledge the following who have played significant roles in this achievement. My supervisor, Dr. Joel Yarney, who has been a very instrumental guide from the proposal writing to completion of the dissertation. Dr. Verna Vanderpuye who has been a great source of encouragement. My senior colleague, Dr. Hanna h Ayettey- Anie and dear friend Dr Naa Adorkor Aryeetey who encouraged and supported me.

Mr. Charles Aidoo graciously assisted in retrieving patients' folders for data collection, without whose help the statistical work would have been a challenge, I am deeply indebted to several other members of staff at the Centre who offered assistance in various ways. I am grateful to all of them. I wish to also place on record the work of Dr Georgina Hammond who willingly, joyfully and tirelessly supported me with data entry.

The constant encouragement, moral support and prayers of my husband, Dr Leslie Nii Quarcoopome was moving. He together with my children Jason Quarcoopome and Lesley-Ann Quarcoopome made sure I was refreshed with loving kindness to face numerous challenges that came my way. They were the "cheer" group for me. I thank them all and several others too numerous to mention. With all that support, I never gave up.

To all the above, I dedicate this work to the glory of God.

Principal Investigator: DR MARY - ANN DADZIE

SPECIALIST, RADIOTHERAPY AND ONCOLOGY

NATIONAL RADIOTHERAPY, ONCOLOGY AND NUCLEAR MEDICINE CENTRE

KORLE BU TEACHING HOSPITAL

P.O.BOX KB369 KORLE BU, ACCRA

TELEPHONE 0302669202, 0302676222

FAX 0302676221

maryjayles@yahoo.com

SUPERVISOR: DR JOEL YARNEY

CONSULTANT, RADIOTHERAPY AND ONCOLOGY

NATIONAL RADIOTHERAPY, ONCOLOGY AND NUCLEAR MEDICINE CENTRE

KORLE BU TEACHING HOSPITAL

P.O.BOX KB369 KORLE BU, ACCRA

TELEPHONE 0302669202, 0302676222

FAX 0302676221

kodwoahen@gmail.com

ABSTRACT

Background: Endometrial cancer accounted for 16.8% of all cancers at the National Radiotherapy, Oncology and Nuclear Medicine Centre, Accra, Ghana between 2009 and 2018, making it the second most common female genital tract cancer seen at the centre.

Patients diagnosed with early-stage disease have good prognosis after surgery alone. However, in patients who have a high risk for recurrence, a good balance is required to improve therapeutic index by selecting effective, individualized adjuvant therapies while at the same time avoiding overtreatment with accompanying short and long-term toxicities.

Although recently there have been significant advances in the understanding of endometrial cancer biology, the role of lymphadenectomy, adjuvant radiation, and chemotherapy is still not well defined. As a result, variability in the management of endometrial cancer across oncology centres is common and may have an impact on outcomes. There is limited literature on the current incidence of endometrial cancer, its detailed clinicopathological pattern, prognosis and practices in the management of endometrial cancer from Ghana. Lack of such information hampers the development of strategies to improve the outcome.

Aim: To assess the treatment outcomes and factors affecting recurrence and survival in endometrial cancer patients treated with curative intent at the Korle Bu Teaching Hospital from January 2009 to December 2018.

Methodology: In this retrospective study, data on patients with histological diagnosis of endometrial carcinoma seen at the National Radiotherapy, Oncology and Nuclear Medicine Centre treated between 1st January 2009 and 31st December 2018 were retrieved from the database. All patients had total abdominal hysterectomy with or without pelvic +/- para-aortic lymphadenectomy/sampling. Adjuvant therapy included external beam radiotherapy (EBRT) on cobalt- 60 machine +/-vaginal brachytherapy either with low or high dose rate +/- chemotherapy depending on risk stratification. Information regarding the demographic, clinical and pathological status of patients, type and sequence of treatment and follow-up of the patient after treatment was retrieved from the patients' medical records. Patients that met the inclusion criteria were assessed. They were then categorized into risks groups based on the PORTEC definition and analyzed for

the following endpoints: loco-regional and distant recurrence rates, the overall and disease–free survival rates, and factors affecting recurrence, disease-free and overall survival.

Results: A total of 146 out of 269 patients were eligible for the study. The mean age was 61.3 years with majority being postmenopausal (77%) and a high prevalence of hypertension (42%) and diabetes (20%). The commonest presentation was abnormal vaginal bleeding (79%) and major histological type was endometrioid adenocarcinoma (78%). All patients had total abdominal hysterectomy with bilateral salpingo-oophrectomy with a lymph node dissection rate of 11% and a lymph node positivity rate of 62.5%. Less than half (47%) were FIGO stage 1. The 5year overall survival was 87.5%, 69%. 57% and 30% respectively for low, intermediate, high Intermediate and high risk patients (P-value: 0.001) whiles that for disease-free survival was 67%, 59%, 64.5% and 54% (P- value: 0.74). Adjuvant radiotherapy resulted in significantly improved 2year disease-free survival compared to those who had no radiotherapy in intermediate (100% vs 54% p-value: 0.006), high intermediate (87.5% vs 63%, p-value:0.041) and high risk (70.5% vs 45.5% p-value :0.041) but not overall survival. There was no difference in disease free and overall survival between patients who had pelvic lymphadenectomy and those who did not. After a median follow up of 34.5 months, there were 51 (35%) recurrences, majority of which were pelvic. Lymphovascular space invasion was the only factor associated with recurrence(p-value:0.01) whiles FIGO stage (P-value: 0.05), grade(p-value:0.03) and histology(p-calue:0.02) were associated with survival. Marital status was the only sociodemographic factor associated with survival

Conclusion: Overall survival outcome for patients with endometrial cancer is comparable to developed countries but not disease-free survival which was poorer due to high recurrence rate. Adjuvant radiotherapy significantly improved the disease-free survival notably in intermediate risk population. Novel molecular testing is needed to better risk stratify and select patients who will benefit from adjuvant therapy to mitigate the high pelvic recurrences observed in the study.

Keywords: Endometrial cancer, risk stratification, adjuvant radiotherapy, Loco-regional recurrence, Distant recurrence. Overall survival, Disease-free survival.

Table of Contents

List of Tables

List of Figures

ABBREVIATION

BMI – Body Mass Index

BSO - Bilateral salpingo -oophorectomy

CL – Copy Low

CRT – Chemoradiation

DFS - Disease-free survival

EBRT – External Beam Radiotherapy

EC - Endometrial cancer

FFS – Failure free survival

FIGO - International Federation of Gynaecology and Obstetrics

GOG - Gynecologic Oncology Group

HIR - High-intermediate risk

IMA- Inferior mesenteric artery

IMRT- Intensity Modulated Radiotherapy

LVSI - Lymphovascular invasion

LNMC- Lifetime number of menstrual cycles

MMI - Myometrial invasion

MMR-D - Mismatch repair deficient

MSI – Microsatelite instability

mTOR - Mammalian target of rapamycin

NSMP - ‘no specific molecular profile’

OS - Overall survival

ProMisE - Proactive Molecular Risk Classifier for Endometrial Cancer

RT – Radiotherapy

SEER - Surveillance, Epidemiology, and End Results

SLN - Sentinel lymph node

TCGA - Cancer Genome Atlas

VBT – Vaginal brachytherapy

VMAT- Volumetric Arc Therapy

CHAPTER ONE

1.1 Background

Endometrial cancer (EC) is the second most prevalent gynecologic cancer in the world, but it is the most common in high-income countries. [1] It appears to be the most common female genital tract malignancy in North Africa, as it is in the Western world.[2] However, in Sub-Saharan Africa, it is the third most prevalent malignant tumor of the female genital tract**.** Endometrial cancer accounts for 4–11 percent of all genital tract malignancies, based on a recent audit in Nigeria. [3] According to the Accra cancer registry, this malignancy ranked second to cervical cancer in 2017, with an age standardized incidence rate of 5.7 per 100,000 population.[4] Similarly, it accounted for 16.8% of all gynaecologiocal malignancies at the National Radiotherapy, Oncology, and Nuclear Medicine Centre between 2009 and 2018, making it the second commonest female genital tract cancer.

Endometrial malignancies are more prevalent in postmenopausal women, and the most common symptom is vaginal bleeding with or without discharge. [5] The most prevalent histological form is pure adenocarcinoma, which accounts for 80% of occurrences, while clear cell and papillary serous tumors account for 20% of cases.[5] Endometrial sarcoma is extremely rare, occurring in only approximately 1% of cases in the Western world. [6]

Endometrial cancer has an aetiology that is unknown. However, various risk factors have been linked to it, the most prominent of which is unopposed oestrogen[7,8]. Early menarche, late menopause, tamoxifen medication, nulliparity, failure to ovulate, and polycystic ovarian syndrome are all examples of this. Age, obesity, hypertension, diabetes mellitus, and genetic nonpolyposis colorectal cancer are also additional risk factors. [9,10]

Hysterectomy is the standard treatment for most endometrial cancers. The uterus, fallopian tubes, and ovaries are removed during surgery, as well as peritoneal cytology and intraoperative examination of the pelvic and para-aortic lymph nodes. For the past couple of decades, this has been the standard of care for the majority of women with endometrial cancer. Although the overall prognosis for women with surgically treated EC is favorable, Bendifallah et al[11] recently observed that at least 20% of these women will have a recurrence, with 70% to 75% of these recurrences

occurring in the vaginal area. More than 70% of recurrences occur within the first 2 to 3 years following first therapy, according to research. [12] In PORTEC-1, the 3-year OS rate in patients previously treated with adjuvant radiotherapy was 43%, significantly lower than the 65% observed for RT-naive patients with isolated vaginal recurrences[13], and 57% and 19% respectively, for regional and distant recurrences. The purpose of treatment for women who recur with distant metastases is palliative care.

The most crucial decision in care is evaluating the related pathologic data such as stage, grade, and lymphovascular space invasion for adjuvant therapy in patients with a high probability of recurrence after surgery. In the adjuvant treatment setting, oncologists have three options: systemic chemotherapy, external beam pelvic radiation, or vaginal brachytherapy, each with its risks and side effects.

1.2 Problem statement

Endometrial cancer is expected to increase by more than 50% globally by 2040, according to the International Agency for Research on Cancer. [14] It is the only gynecologic cancer with a rising incidence and fatality rate in the United States. [15] Endometrial cancer has racial differences, with white women having a 5-year relative survival rate of 84% and black women having a 5-year relative survival rate of 62% in 2018. [16] The greater incidence of advanced stage, high grade, aggressive histology tumors and poor access to healthcare in black women is thought to be the cause of these discrepancies. [1]

The vast majority of individuals identified have early-stage cancer with a favorable prognosis after surgery is performed alone.[18] However, in patients with a high risk of recurrence, such as is seen in many black women [17], finding a good balance between selecting effective, tailored adjuvant therapy while avoiding overtreatment is crucial. Adjuvant treatment recommendations such as radiotherapy and systemic therapy remain complicated and controversial. The majority of endometrial cancer studies are conducted in western countries, with indigenous Africans being underrepresented, leaving many concerns unsolved in this group. All adjuvant therapy protocols for indigenous African women are based on trials that do not fully represent them. With advances in cancer biology and genetics, it is now widely accepted that race

and ethnicity play a role in cancer incidence, natural history, and treatment outcomes. Extensive literature search yielded no research done to describe the clinicopathology and treatment outcome of endometrial cancer in Ghana.

1.3 Aim

To assess the treatment outcomes and factors affecting recurrence and survival in endometrial cancer patients treated with curative intent at the Korle Bu Teaching Hospital from January 2009 to December 2018.

1.4 Objectives

1. To describe the sociodemographic characteristics of patients with endometrial cancertreated at the National Radiotherapy Oncology and Nuclear Medicine Centre.
2. To compare occurrence of known risk factors in endometrial cancer patients in the study group to the occurrence of the risk factors in the general population.
3. To determine the treatment outcome by stage - disease-free survival (DFS) and overall survival (OS) of endometrial cancer patients at 2 and 5 years according to risk groups and treatment received.
4. To estimate the locoregional and distant recurrence rate after treatment for endometrial cancer.
5. To examine the sociodemographic, clinico-pathological and treatment related prognostic factors associated with recurrence and survival in order to make recommendation for treatment.

1.5 Justification

It has recently been suggested that the incidence of endometrial malignancies is rising in Sub-Saharan Africa, owing to improvements in diagnostic facilities, particularly ultrasonography and histopathological services, as well as an increase in the population of perimenopausal/menopausal women with low parity[1]. Despite substantial breakthroughs in our understanding of endometrial cancer biology, the role of lymphadenectomy, adjuvant radiation, and chemotherapy in the treatment of endometrial cancer is still unclear.

As a result, variability in the management of endometrial cancer across centers is common. This variability may have an impact on outcomes. There is limited literature on the current incidence of endometrial cancer, its detailed clinicopathological pattern and outcome of endometrial cancer from Ghana. Lack of such information hampers the development of strategies to improve prognosis. This retrospective review was planned to evaluate the outcomes of endometrial cancer patients treated at the National radiotherapy, Oncology and Nuclear Medicine Centre from 1st January 2009 to 31st December 2018. The results of this study will allow us make recommendations for treatment in order to improve patient outcome.

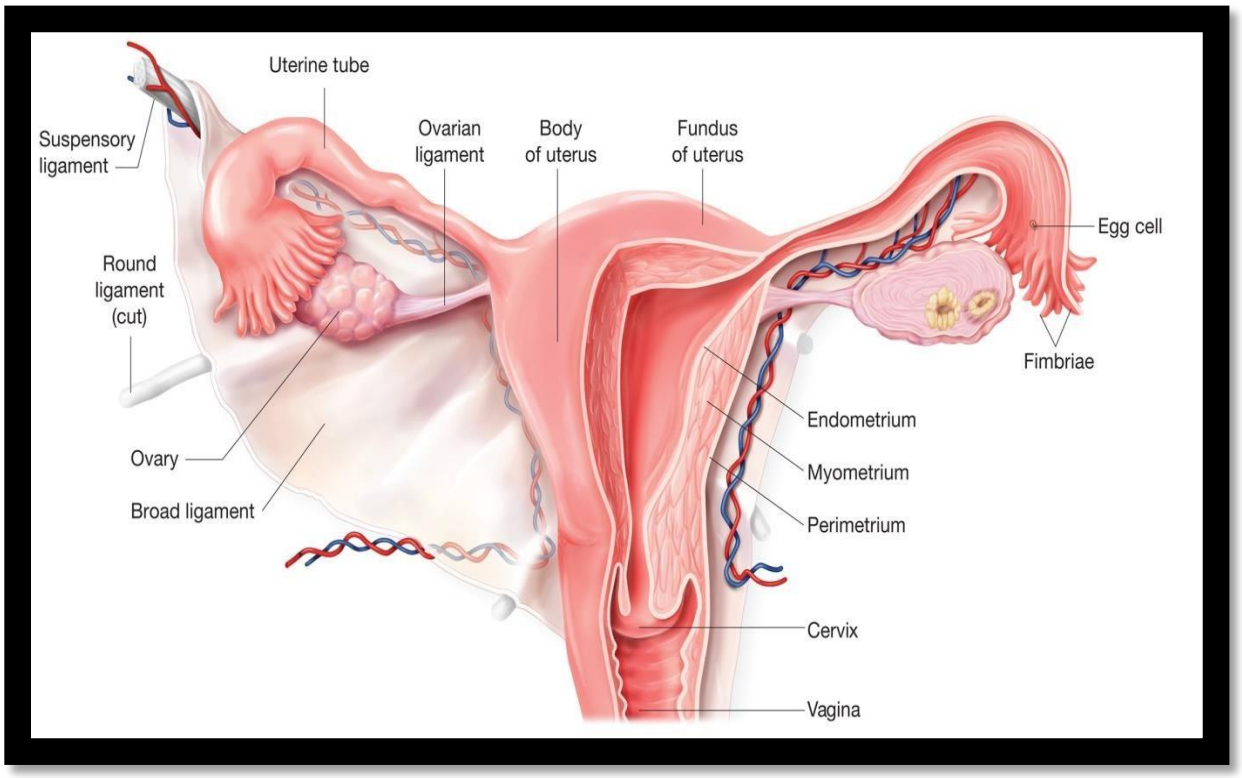
CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 The Uterus

The uterus is a hollow, muscular organ found between the bladder and the rectum in the true pelvis. The average adult uterus is 8 centimeters long, 5 centimeters broad, and 2.5 centimeters thick. The fundus, body (corpus), and cervix are the three parts of the uterus. The isthmus is the connection between the body and the cervix. The fallopian tubes puncture the fundus at each cornu. Peritoneum partially covers the uterine surface. Endometrium, which is made up of columnar cells that form numerous tubular glands, lines the uterine cavity. The thickness of the endometrium varies throughout the menstrual cycle, but it should be 2 to 3 mm thick towards the end of menstruation. Myometrium, made up of smooth muscle fibers, makes up the uterine wall. The broad, round, uterosacral, and cardinal ligaments are the main supports of the uterus. The uterine artery, which enters the uterus at the isthmus after crossing the ureter, is the main blood supply. The obturator and internal and external iliac lymph nodes are the primary lymphatic drainage sources for the uterus's body. The ovarian artery, accompanied by lymphatics from the fundus, drain directly into the para-aortic lymph nodes.

Figure 1: Anatomy of The Uterus



2.2 Endometrial Cancer

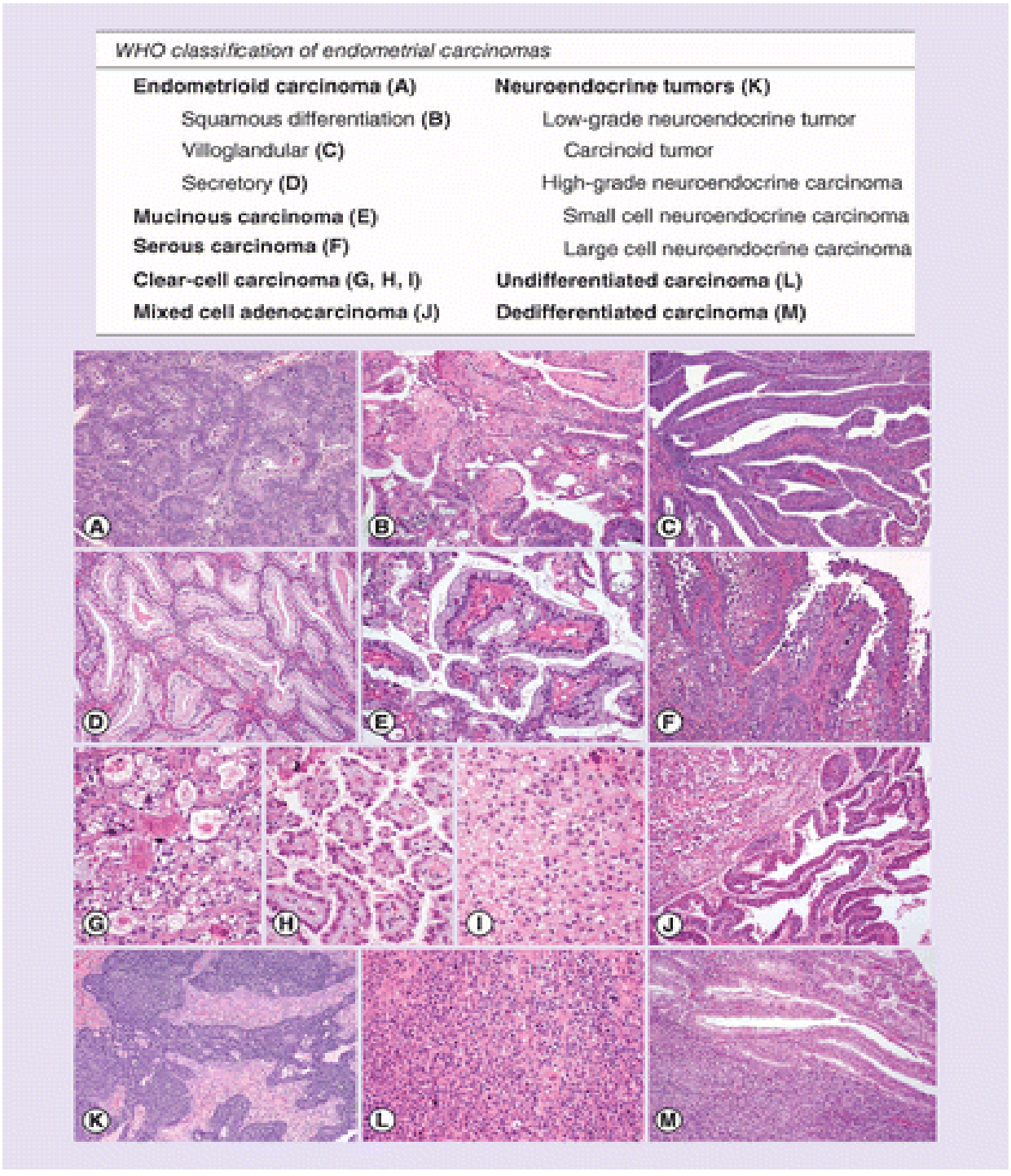
During the reproductive years, the endometrium, a specialized tissue in the uterine cavity undergoes substantial histological changes during each menstrual cycle. During each cycle, trophic hormones stimulate the endometrium to grow normally and eventually change it into a secretory endometrium with active mucin synthesis. Oestrogen and progesterone are the two hormones that control the endometrial cycle. Progesterone stimulates luteinisation and mucin secretion (secretory phase), while oestrogen causes growth (proliferative phase). Excessive oestrogen production leads to over stimulation of the endometrial stratum functionalis, and if typical secretory phase endometrial alterations do not occur under the influence of progesterone, regular endometrial shedding is absent, which can lead to hyperplastic and malignant abnormalities. Unopposed oestrogen is substantially linked to an increased risk of endometrial cancer, according to several lines of evidence. Patients with granulosa-theca cell tumours of the ovary, for example, have a greater risk of developing endometrial cancer.[19,20]

Endometrial adenocarcinoma accounts for roughly 90% of all uterine cancers, followed by uterine sarcoma (8%), which arises from the outer layer (myometrium), and other cancers that are less common (2%). [21]

They are more prevalent in postmenopausal women, affecting women in their sixth and seventh decades of life [22], and the most common symptoms are vaginal bleeding with or without discharge.[23] Endometrial sampling via hysteroscopy or, less typically, vacuum aspiration is the gold standard for diagnosis. Endometrioid-type adenocarcinoma is the most prevalent histological type, however there are also mucinous adenocarcinoma, clear cell carcinoma, uterine papillary serous carcinoma, squamous carcinoma, and carcinosarcoma.[21] (See Figure 2)

Hysterectomy, traditionally is the initial treatment for endometrial carcinoma. The uterus, fallopian tubes, and ovaries are removed during surgery, as well as peritoneal cytology and intraoperative examination of the pelvic and para-aortic lymph nodes. Surgery alone is adequate for patients with early disease and provides a fair outcome. However, in patients with a high risk of recurrence, adjuvant therapy (systemic therapy and radiation therapy) mast be tailored towards achieving excellent disease control while minimising side effects.

Figure 2: Histological Types of Endometrial cancer



2.3 Risk factors

Several risk factors have been identified in epidemiological research and linked to an increased risk of endometrial cancer. These risk factors are based on probabilities, so that women who have none of them, could still develop endometrial cancer. Endometrial cancer has been linked to age, BMI, race, familial history, and polycystic ovary, as well as diet, physical activity, smoking, parity, breastfeeding, hormone-replacement therapy, hypertension, diabetes, socioeconomic status, and exposure to infertility treatment, causing several controversies in terms of incidence and mortality. [24]

The risk of endometrial cancer is observed to be positively correlated to age.[25] With almost 90% of cases detected after the age of 50, the condition is more common in postmenopausal women than in premenopausal women. [26] Because of increased life expectancy and lifestyle, the incidence of endometrial cancer is higher in industrialized countries than in most developing ones. [27]

Endometrial cancer incidence and mortality rates differ between races, according to data from Western countries. Caucasian women are more likely than women from other ethnic groups to develop endometrial cancer. [28] Although African American women are 30 percent less likely than Caucasian women to develop endometrial cancer, they are more likely to present with advanced stage tumour, resulting in a fourfold increase in mortality when compared to their white counterparts. [28] Poor access to health care, advanced stage at diagnosis, tumour characteristics, and treatment delay are all factors that increase the risk of death in black women. [28] This is a common occurrence in Ghana and other developing countries.

Menarche occurring early in life, while menopause occurring later in life, increases the number of menstrual cycles and, as a result, the overall amount of oestrogen exposure time. When compared to women who reach menarche at or after the age of fifteen, those who reach menarche earlier have a nine-fold increased chance of having endometrial cancer. [29] Women who went through menopause between the ages of 50 and 54 had a 67% higher risk of endometrial cancer than women who went through menopause before the age of 45, according to Setiawan and colleagues.[30] When menopause happened after the age of 55, the risk increased by 79%. [30]

Obesity has been linked to endometrial cancer in both pre-menopausal and post-menopausal women.[31] Excess adipose tissue converts testosterone to oestrogen, resulting in an increase in circulating endogenous oestrogens. [32] When obesity is combined with infertility or amenorrhoea, the risk of developing endometrial cancer rises.[33] This is due to the fact that obesity increases insulin resistance and oestrogen exposure, both of which are already high in infertile women and women who have anovulation or amenorrhea.[34] When compared to women with a normal BMI, obese women have a 2–22 times increased risk of endometrial cancer.[35] For every 5 kilograms gained, the risk of endometrial cancer rises by 1.2 times.[36]

Hypertensive women have a 3-fold increased risk of developing endometrial cancer compared to healthy women. It's unclear if this positive relationship is attributable to hypertension or its interaction with weight, because the link between hypertension and endometrial cancer risk usually disappears after body weight is taken into account.[37]

Diabetes has been linked to an increased risk of endometrial cancer in studies.[38] Diabetic women have a 2 to 3 times higher risk of developing endometrial cancer than non-diabetic women.[39] Patients with Type 2 diabetes are more likely to be obese, whereas women with Type 1 diabetes are more likely to have nulliparity, irregular menstruation, and infertility, all of which are potential risk factors for endometrial cancer.[40] When diabetes is combined with obesity, Friberg and colleagues discovered a sixfold increase in the risk of endometrial cancer, and a tenfold increase when obese diabetic women do not exercise.[41]

2.4 Classification of Endometrial Cancer

The first subclassification of endometrial carcinoma was based on anatomic location, distinguishing tumours of the endometrium from malignancies of the cervical cavity. Subsequent subclassification was based on cell type, which corresponded to the Type I and Type II groups found by Bokhman thirty years ago in his epidemiological investigations.[42] Endometrioid carcinoma was assigned to Type I, while serous carcinoma was assigned to Type II. Type 1 tumours are endometrioid, low grade, diploid, hormone-receptor positive tumours that are

moderately or well-differentiated, and are more common in obese women (70–80 percent). Patients with Type 1 tumours usually have localized illness that is limited to the uterus and have a good prognosis. Type 2 tumours (20–30%), on the other hand, are more common in non-obese women, have non-endometrioid histology, are high-grade, aneuploid, poorly differentiated, hormone receptor negative, and have a higher risk of metastasis and poor prognosis.[42]

These histological classifications are difficult to distinguish in practice, owing to significant inter-observer variability in histologic diagnosis, particularly in high-grade tumours. In an attempt to improve subclassification, studies of immunomarkers and then mutational studies of specific genes followed histologic classification. While there are significant distinctions in protein expression and mutation patterns between endometrioid and serous carcinomas, there is also a lot of overlap, therefore subclassification of endometrial carcinoma remains difficult. Endometrial malignancies were subjected to gene panel testing using next-generation sequencing, which revealed that there are tumours with genetic changes intermediate between Type I/endometrioid and Type II/serous carcinomas.

Endometrioid and serous carcinoma studies from the Cancer Genome Atlas (TCGA) provided significant insight into the subclassification of endometrial carcinoma, revealing that there are four separate kinds of endometrial carcinoma, rather than two, based on genomic architecture. This is the most thorough molecular investigation of ECs to date. The project used a combination of whole genome sequencing, exome sequencing, microsatellite instability (MSI) assays, and copy number analysis[43] to classify 236 endometrioid and serous endometrial cancers into four groups: POLE ultramutated, MSI hypermutated, copy-number (CN) low, and CN high - that correlate with progression-free survival.[43]

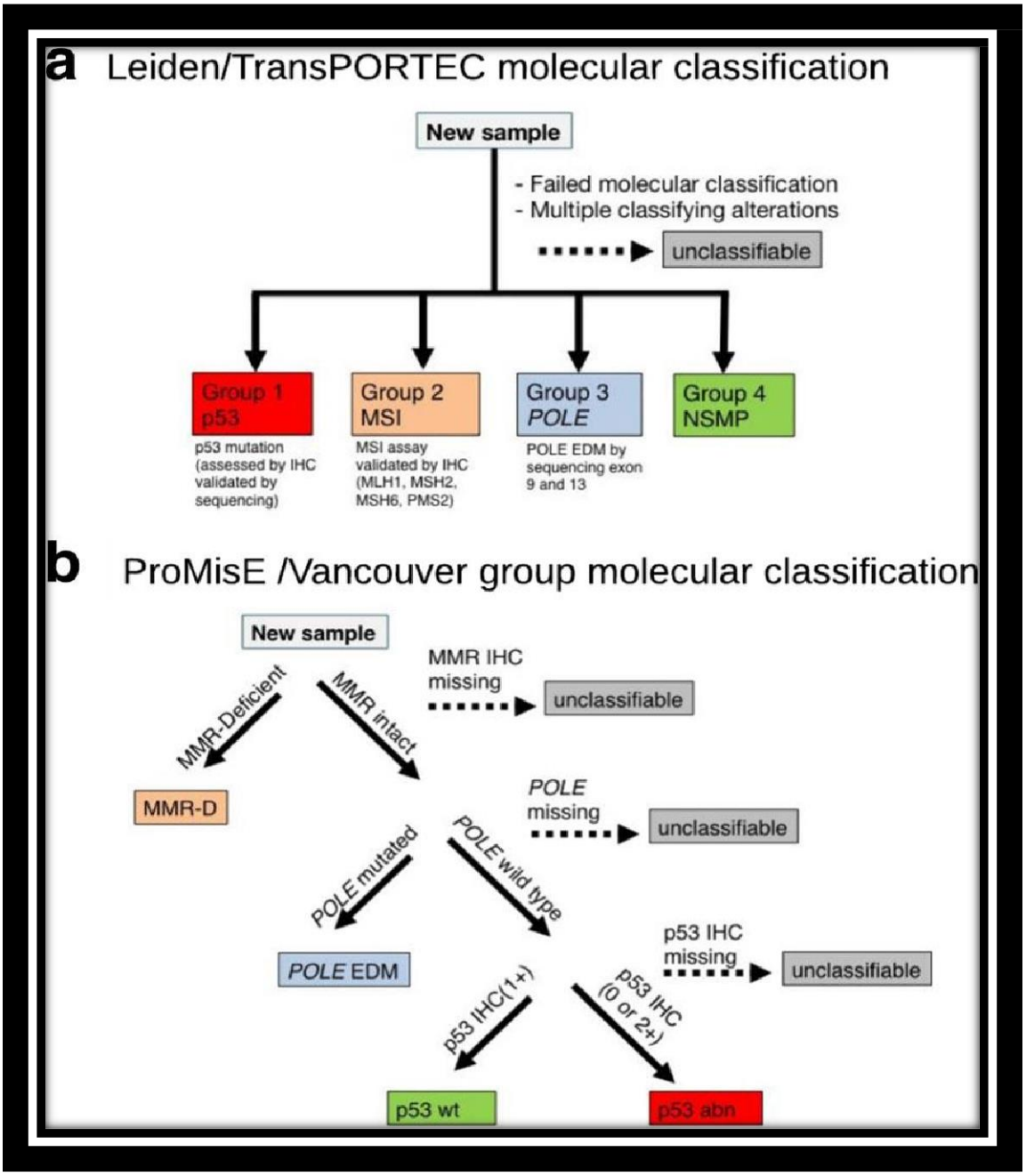
The ultramutated POLE subgroup was a new discovery from the TCGA, and it sparked interest because of its excellent prognosis even in high-grade malignancies.[43] Microsatellite instability (MSI) was also described by TCGA as a molecular subgroup. MSI is caused by flaws in the DNA mismatch repair system after replication. Finally, using copy number analysis, TCGA identified a separate molecular subgroup that was classified between "high" and "low."[43] Endometrial tumours can be classified into one of four prognostic groupings using objective

molecular classification. The methodologies used in the TCGA study, on the other hand, are expensive, difficult, and inappropriate for wider clinical usage.

Following that, two research groups developed more practical methodologies for evaluating molecular features in standard formalin-fixed paraffin-embedded tissue. The Leiden/TransPORTEC group testing resulted in four molecular subgroups: group 1 – p53 (mutation discovered), group 2 – MSI, group 3 –POLE (POLE EDM identified), and group 4 – NSMP (no specific molecular profile).[44] They discovered that patients in the POLE and MSI subgroups had similar and substantially better survival results than those in the p53 mutant and NSMP groups, who had worse recurrence and distant metastatic outcomes even in endometrioid histology instances.[44]

The ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) team also identified 4 subgroups: Group 1: Mismatch repair deficient (MMR-D) 2), Group 2: POLE exonuclease domain mutations ('POLE EDM'), Group 3: p53 wild type (p53wt), and Group 4: p53 null or missense mutations (p53+abn).[45] Clinicopathological characteristics of women in each molecular grouping have been reliably demonstrated to be typical of that group. For example, the p53abn subgroup appears in older, thinner women and has the highest proportion of high grade, advanced stage non-endometrioid histotypes. Women in the POLE EDMs subgroup are of particular interest because they tend to be younger, thinner, and have surprisingly aggressive pathologic features (a high proportion of grade 3 tumors, many with deep myometrial invasion and lymphovascular invasion (LVSI)), but they consistently have good outcomes.[46]Despite having extremely similar clinicopathologic traits[47] to the POLE subgroup, such as similar proportion of high-grade tumors, deep myometrial invasion, and LVSI, the MMR-D subgroup has the worst observed outcomes of any group other than p53abn.[48]

Figure 3: Leiden/TransPORTEC and b ProMisE/ Vancouver molecular classification systems.



The incorporation of biologically relevant molecular information into EC diagnosesallows for treatment classification based on molecular subclasses. Depending on the clinical context, this integrated information may be used to guide therapy in the preoperative, postoperative, and recurring or metastatic settings. It may also contain information that can be usedfor surveillance recommendations or targeted treatment alternatives.

One of the most difficult aspects of the proposed molecular endometrial cancer stratification is determining how to identify and manage tumours with numerous molecular features, often known as 'multiple classifiers.' Multiple classifiers are utilized in a small percentage of endometrial cancer cases, ranging from 3% to 5% in the published series that used surrogate markers. The TCGA, on the other hand, found a greater frequency, which is most likely due to the differences in how the subgroups were classified.[43]

The clinical outcome data is insufficient to assign these multiple classifiers to one of the molecular subclasses. Knowing the clinical behaviour of these numerous classifiers will be critical in guiding therapy selections. To address this problem, international collaboration is ongoing. The findings of the PORTEC-4 phase III randomized trial of molecular-integrated risk-based adjuvant treatment of EC could help resolve some of these issues.

The TCGA's molecular categorization was based on EC with endometrioid and serous morphology, therefore whether it can be applied to other rare endometrial cancer subtypes remains to be seen.

2.5 Staging

In 1958, the International Federation of Gynaecology and Obstetrics (FIGO) created a classification and staging system for endometrial cancer and other female genital cancers.[49] This endometrial cancer staging system was mainly clinical until 1988. Tumours localized to the uterus were classified as stage I, with IA if the length was less than 8 cm and IB if the length was greater than 8 cm. Stage II was for when the cervix was affected, stage III was for when disease extended

beyond the uterus/cervix and was limited to the true pelvis, and stage IV was for when it spread beyond the true pelvis, involved the bladder or rectum (IVA), or beyond the pelvis (IVB).[49]

The Gynaecologic Oncology Group (GOG) conducted research in 1984 on clinicopathologic variables and recurrence patterns in clinical stage I endometrial cancer.[50] To further explore these characteristics, a larger prospective experiment (GOG 33) looked at 621 women with clinical stage I endometrial cancer[51] who had total abdominal hysterectomy/bilateral salpingo-oophorectomy, peritoneal cytology, and selective pelvic and para-aortic lymphadenectomy.[51] A total of 144 (22%) of the 621 patients had disease outside the uterus. Positive peritoneal cytology was seen in 12% of cases, adnexal involvement in 5% of cases, and regional lymph node involvement in 11% of cases. Pelvic node metastases were discovered in only 3% of patients with grade 1 endometrium-confined disease, but in more than 30% of patients with grade 3 tumours that involved the outer one-third of the myometrium. Aortic nodal disease was detected in 14% and 23% of patients with deeply invasive grade 2 or 3 disease respectively. This exposed some of the flaws in the clinical staging approach, prompting FIGO to establish a surgical staging method in 1988 in order to better estimate patients' 5-year prognoses and better tailor adjuvant therapy to those most likely to benefit from it (Table 1).

The FIGO staging system was modified once more in 2009.[52] Patients who were previously classified as IB (<50 percent myometrial invasion) are now classified as IA. Patients that have more than 5 0% myometrial invasion are classified as stage IB. Only patients with cervical stromal invasion are classified as stage II, regardless of endocervical glandular involvement. The presence of positive peritoneal cytology no longer has an impact on staging. Parametrial extension is now classified as a type IIIB condition. Patients with stage IIIC are now separated into two groups: IIIC1 for pelvic nodes and IIIC2 for para-aortic nodes (Table 2).

Table 1: FIGO 1988 endometrial cancer staging

STAG E	ANATOMIC INVOLVEMENT
Stage 1	Tumour confined to uterine corpus
1A	No myometrial invasion
1B	< 50% myometrial invasion
1C	≥50% myometrial invasion
Stage II	Cervical involvement
IIA	Endocervical glandular involvement
IIB	Cervical stromal involvement
IIIA	Positive peritoneal cytology and/or tumor invasion into uterine serosa and/or adnexal involvement
IIIB	Vaginal involvement
IIIC	Metastasis to pelvic and /or para-aortic lymph nodes
IVA	Bladder and /or bowel involvement
IVB	Disease metastasis including abdominal metastasis and /or inguinal lymph node involvement

Table 2: FIGO 2009 endometrial cancer staging

STAGE	ANATOMIC INVOLVEMENT
Stage 1	Confined to uterine corpus
IA	Tumor limited to the endometrium or < 50% of the myometrium (includes endocervical glandular involvement)
IB	Invasion to ≥50% of the myometrium (Includes endocervical Glandular involvement)
II	Cervical stromal invasion
IIIA	Tumour invades uterine serosa or adnexa
IIIB	Tumour involves vagina and /or parametria
IIIC	Pelvic and /or para – aortic lymph node involvement
IIIC1	Pelvic lymph node involvement
IIIC2	Para –aortic lymph node involvement with or without pelvic lymph nodal involvement
Stage IV	
IVA	Invasion of bladder, bowel mucosa or both
IVB	Distant metastasis, including intra- abdominal spread or Inguinal lymph nodes.

2.6 Surgery and its controversies

Surgical staging has long been a part of the initial management of endometrial cancer, as it is required for prognostic classification as well as the identification of patients who might benefit from chemotherapy or radiation therapy (RT). Total extrafascial hysterectomy, which includes the removal of the uterus and cervix as well as bilateral salpingo-oophorectomy (BSO), is a common procedure that can be performed using minimally invasive or open techniques. Lymph node evaluation is advised, with suspicious-appearing lymph nodes being removed at the very least. Wherever possible, gross extrauterine disease should be biopsied and removed. Given the increased risk of advanced-stage disease at diagnosis and relatively low morbidity with the procedure, omentectomy may be considered for clear cell, serous, and occasionally carcinosarcoma histologies, though the risk of microscopic involvement in the absence of visible macroscopic disease is low.[53,54]

Traditional Lymphadenectomy

Historically, total pelvic and para-aortic lymphadenectomy were used to stage endometrial cancer. For apparent uterine restricted disease, the National Comprehensive Cancer Network suggests "lymph node examination." This word has spawned a plethora of practice patterns as well as debate over the scope and strategy of lymphadenectomy.[55] Lymph node examination "includes evaluation of the nodal basins that drain the uterus, and generally requires a pelvic nodal dissection with or without para-aortic nodal dissection," according to the National Comprehensive Cancer Network.[55] However, according to the European Society for Medical Oncology, lymphadenectomy (the systematic removal of pelvic and para-aortic nodes up to the level of the renal veins) is not recommended for low-risk, grade 1 or 2 disease, but it "can be considered" with sentinel lymph node dissection for myometrial invasion (MMI) >50 percent for grade 3, and all stages of nonendometrioid histology. [56] A staging lymphadenectomy is defined as the bilateral removal of all nodal tissue with skeletonization of all vessels from the mid-portion of the common iliac vessels superiorly to the circumflex iliac vein inferiorly, from the mid-psoas laterally to the ureters medially, including the obturator fossa, according to the Gynaecologic Oncology Group (GOG) Surgical Procedures Manual. From here to the level of the inferior mesenteric artery, marks

the area for para-aortic dissection (IMA).[57] Unresectable nodes should be identified with clips for possible radiotherapy (RT) planning, and visible or suspicious-appearing nodes should be excised at a minimum.

The selection of patients for routine surgical lymph node staging, as well as the scope of the staging, is a contentious issue. The absence of confirmed survival advantages to lymphadenectomy is cited by those who advocate for no lymphadenectomy and limit nodal assessment to inspection and removal of any enlarged/suspicious pelvic or para-aortic nodes. In addition, patients with pathologic characteristics that raise the chance of microscopic lymph node metastases are often given adjuvant pelvic radiation. Full pelvic and para-aortic lymph node sampling proponents argue that surgical staging is the most accurate way to determine the extent of disease because palpation of lymph nodes has only 72 percent and 81 percent sensitivity and specificity, respectively.

Optional Lymphadenectomy

Another strategy is optional lymphadenectomy, in which preoperative tumour grading combined with intraoperative assessment of depth of myometrial invasion and histologic subtype is usually used to determine if lymph node dissection is required at the time of hysterectomy. Patients with grade 3 illness, serous or clear-cell histology, and deep myometrial invasion on frozen section will undergo lymphadenectomy using this approach. Opponents of selective lymphadenectomy point out that the depth of myometrial invasion correlates with final stage diagnosis of endometrial cancer in only 67 percent of cases[59] and only 85 percent of preoperative FIGO grade 1 diagnosis correlates with final grade diagnosis of endometrial cancer in only 85 percent of cases.[60]

Despite the debates regarding optional or no lymphadenectomy, many surgeons have remained skeptical of full lymphadenectomy because of the findings of two large randomized control studies that failed to show a survival benefit. The first was an Italian trial with 514 eligible patients with preoperative FIGO grade I endometrial cancer who were randomly assigned to pelvic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250) in an Italian study.[61] In the pelvic lymphadenectomy arm, the median number of lymph nodes removed was 30. In an intention-to-

treat analysis, the 5-year disease-free and overall survival rates were identical between groups after a median follow-up of 49 months (81.0 percent and 85.9 percent in the lymphadenectomy arm and 81.7 percent and 90.0 percent in the no-lymphadenectomy arm, respectively).

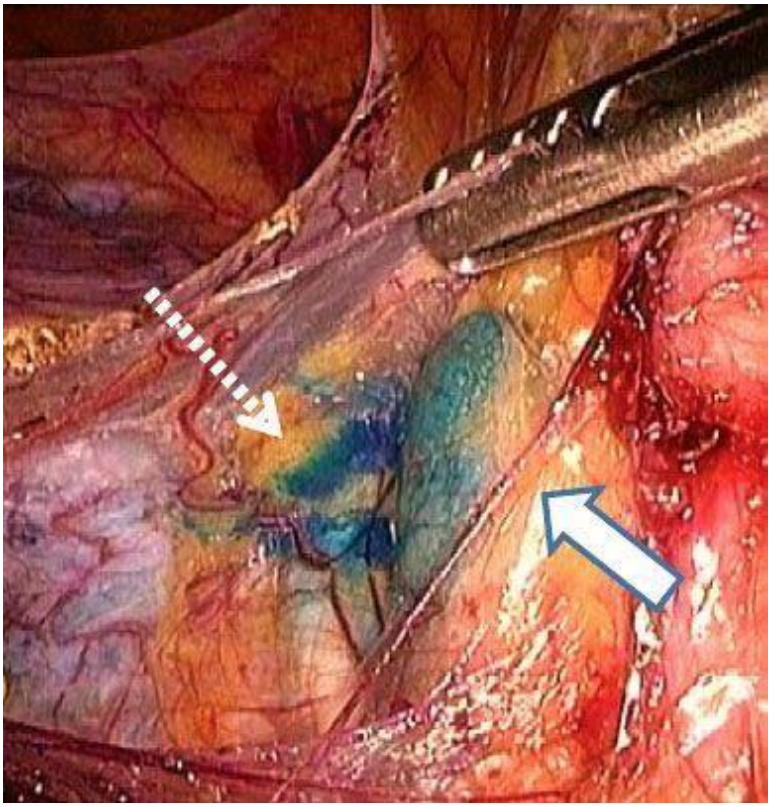
The UK Medical Research Council-A Study in the Treatment of Endometrial Cancer (MRC-ASTEC) was the second. Patients with endometrial cancer restricted to the uterine corpus were first randomized to lymphadenectomy (n = 704) or conventional surgery (hysterectomy-BSO, pelvic washing, and probing of para-aortic nodes). Patients in the lymphadenectomy group had surgery combined with thorough dissection of iliac and obturator nodes. The surgeon had complete discretion over whether or not to dissect the para-aortic nodes. There was no difference in 5-year disease-free survival after a median follow-up of 37 months.[62] Both trials found that pelvic lymphadenectomy improved surgical staging, indicating that it is a good prognosticator, but it had no effect on disease-free or overall survival.

Sentinel Lymphadenectomy

There has been interest in using a sentinel lymph node technique, similar to that used in breast cancer, as a trade-off between lymphadenectomy and no surgical examination. Because of the difficulty in developing a viable marker dye and the disagreement over procedure, this approach fell behind other disease sites. The highest rate of sentinel lymph node identification has now been linked to cervical injection.[63] The Fluorescence Imaging for Robotic Endometrial Sentinel Lymph Node Biopsy [FIRES] investigated test characteristics of sentinel lymph node biopsy in patients with clinical stage I illness of any histology in a recent prospective cohort analysis. 64 According to the findings, illness was appropriately recognized in 97 percent of patients' sentinel lymph nodes. Six patients (17%) exhibited isolated illness in sentinel lymph nodes outside of a standard dissection field (presacral, internal iliac), indicating that the technique had a therapeutic benefit. In 80 percent of patients, the sentinel lymph node was the most distant node afflicted. The rate of false negatives was 3%. The findings of this study imply that SLN mapping is practical, and that incorporating SLN mapping into surgical staging methods improves the chances of discovering metastatic cancer cells in regional lymph nodes. More research is needed to evaluate whether sentinel lymph node mapping will totally replace lymphadenectomy.

Sentinel lymph node biopsy programs are not well established in many low-resource settings due to lack of specialist training, limited resources, and equipment shortages. There is also very little data published on successful SLNB programs in Africa and no data published in Ghana.

Figure 4: Sentinel lymph node. Solid arrow points to the blue dye in an external iliac node. Dashed arrow points to a lymphatic channel draining to the sentinel node.



2.7 Radiotherapy; Indication and Technique

Despite the fact that postoperative radiation (RT) can greatly lower the risk of local recurrence, randomized prospective trials in early-stage endometrial cancer have not shown an OS benefit. For patients with a low-risk disease, adjuvant treatment should be avoided. Vaginal brachytherapy (VBT) provides good local control at the vaginal cuff for higher-risk patients with early-stage disease. Patients who are locally progressed are usually treated with EBRT to encompass any nodal regions that are at risk. The decision to employ adjuvant RT and the modalities used (VBT and/or EBRT) can be controversial, and it often hinges on the physician's assessment of individual clinicopathologic features.

Low Risk

Low-risk disease, which is commonly described as low- grade disease restricted to the endometrium or with limited MMI, is usually treated successfully with surgery alone.[65]

Intermediate Risk

A large body of evidence, including at least six randomized trials, describes intermediate-risk disease.[66-71] Having any MMI, up to occult stage II disease, or grade 2 or 3 disease is considered intermediate risk. The GOG and the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) group have also defined a high-intermediate risk (HIR) grouping. Those who meet the PORTEC criteria have at least two of the following: they are over 60 years old, they have grade 3 illness, or they have a 50% MMI. Alternatively, the GOG defines HIR according to age and the number of risk factors (grade 2-3, LVSI, or MMI in the outer one-third): Patients above the age of 70 must have one risk factor, those over the age of 50 must have two risk factors, and those under the age of 50 must have all three risk factors. Various clinical trial inclusion criteria and surgical lymph node sampling practice patterns make reaching an integrated therapy recommendation that is consistent across all groups problematic.

In GOG 99 and PORTEC-1[66,67], the benefit of adjuvant RT for HIR tumours was observed. The GOG 99[66] study randomized patients with stage I and II intermediate-risk adenocarcinoma to observation versus EBRT after surgical resection and selective pelvic and para-aortic lymph node

dissection (50.4 Gy). Overall, EBRT was linked to a lower risk of vault and pelvic recurrence. However, subset analysis revealed that individuals with HIR disease benefited the most from treatment. At 24 months, HIR tumours had a nearly 20% absolute risk reduction (26% vs 6% relative hazard, 0.42; 95 percent CI, 0.21-0.83), compared to only a 4% absolute risk reduction for low-intermediate risk tumours. There were no significant differences in 4-year OS (92 percent for RT vs 86 percent for observation; P =.557) or distant relapse as the initial occurrence (5.3 percent vs 6.4 percent, respectively).[66]

When compared to no further therapy following hysterectomy, PORTEC-1[68] showed reduced rates of locoregional failure after 46 Gy of adjuvant EBRT, with 71 percent of recurrences in the no extra therapy arm occurring in the vagina. Long-term follow-up demonstrated locoregional recurrence rates of >20 percent with no additional therapy versus 5 percent in the HIR group following EBRT (at 15-year follow-up: HR, 3.31 [95 percent CI, 1.73-6.35]; P =.0003), similar to GOG 99.[68]

Failures in HIR are more likely to occur at the vaginal cuff, according to evidence from GOG 99 and PORTEC-1. This shows that vaginal brachytherapy (VBT) could be a sufficient and less hazardous adjuvant treatment option. In the PORTEC-2 study, VBT was compared to EBRT for HIR patients.[69] There was no difference in locoregional control or survival. Pelvic failure rates were generally low, albeit they were higher in VBT patients compared to EBRT (3.8 percent vs. 0.5 percent; P =.02).

Patients with stage I intermediate-risk disease are frequently not given both VBT and EBRT. It's also uncertain whether adding VBT to EBRT adds any clinically significant benefit over EBRT alone, given EBRT's outstanding vaginal control rates. In stage II disease, the benefit of combining VBT and EBRT has not been explored in randomized trials, and there is no high-quality evidence to support or reject this technique.

High Risk

The term "high-risk endometrial malignancies" refers to cancers that are stage III/IV or have a high-risk histology (clear cell and serous carcinoma). Because of their worse prognosis compared to other early-stage disease, many practitioners now put markedly invasive, high-grade

stage I endometrioid carcinomas in this group. These individuals were excluded from randomization in the intermediate-risk PORTEC trials, but they are currently included in several high-risk trials. In this group of patients, older studies[72-74] looked at the effectiveness of adjuvant RT against chemotherapy, with similar survival and disease outcomes. In other prospective studies[75-76] both adjuvant therapy regimens (radiotherapy and chemotherapy) were combined in an attempt to optimize both locoregional and distant control. Concurrent, sequential, and sandwich sequencing approaches have all been investigated, and it's unclear whether one is better than the others.[77]

The radiotherapy technique recommended in high-risk, stage III, endometrial cancers is EBRT (either using 3 dimensional, conformal RT or intensity-modulated RT [IMRT]) directed to the pelvis, inclusive of the vaginal cuff, parametria, and lymphatics at risk (with consideration of coverage of the para-aortic lymph nodes) given the high risk of pelvic nodal disease and recurrence risk in this population.

In summary, surgery alone is often used to treat low-risk illness, such as low-grade tumours restricted to the endometrium or with limited MMI. Intermediate-risk disease is usually treated with at least VBT (Figure 5 shows vaginal brachytherapy applicators), with EBRT being used occasionally for HIR disease.

2.8 Chemotherapy

There is a lack of concrete data on which patients benefit from chemotherapy and which chemotherapy regimen/duration is best. Chemotherapy is generally recommended for serous tumours and stage III or higher cancers of any histology. The most widely utilized regimen is carboplatin and paclitaxel.

Adjuvant Chemotherapy vs Radiotherapy

Adjuvant chemotherapy to radiation has been tested in three randomized trials. The Japanese Gynaecology Oncology Group (JGOG) trial[72] randomized 385 patients with stage (FIGO 1988) IC to III endometrial cancer (25 percent with stage III) to pelvic radiation (193 patients) or chemotherapy (25 percent with stage III) (192 patients). Surgery consisted of a hysterectomy with

or without lymphadenectomy[72] Using anteroposterior/posteroanterior (AP/PA) fields, pelvic RT was given at a dosage of 45 to 50 Gy. Every four weeks, patients were given cyclophosphamide (333 mg/m2), cisplatin (50 mg/m2), and doxorubicin (40 mg/m2) for three cycles or more in the chemotherapy arm. Between the two groups, there was no significant difference in progression-free (p =.726) or overall survival (p =.462) rates.

Three hundred and forty patients with stage (FIGO 1988) IC grade 3, stage II grade 3, and stage III (two-thirds of patients) were randomized to radiation or chemotherapy in an Italian trial with a similar design.[73] The 5-year disease-free survival rate was 63 percent in both arms (p =.44), and the 5-year overall survival rate was 69 percent in the radiation arm and 66 percent in the chemotherapy arm (p =.77) after a median follow-up of 95.5 months. Despite taking five cycles of Cytoxan, cisplatin, and doxorubicin, there was no significant difference in outcome.

In GOG 122, 396 patients with stage III to IV cancer were randomized to eight cycles of doxorubicin/Cisplatin(n-194) verses whole-abdomen radiation (n = 202).[74] The primary outcome of this study was progression-free survival. There was a substantial improvement in both progression-free (50 percent vs. 38 percent; p =.007) and overall survival rate (55 percent vs. 42 percent; p =.004) in favour of chemotherapy after a median follow-up of 74 months. As a result of the findings of GOG 122, adjuvant chemotherapy has been adopted as the primary treatment for stage III endometrial cancer.

Because of the stage mismatch between the two arms, the GOG122 trial has received a lot of criticism. There were 28.2 percent more stage IIIA patients in the RT group than in the chemotherapy arm (18 %). In the chemotherapy arm, however, there were more patients with stage IIIC illness (51.5%) than in the RT group (44.6 %). As a result, the 5-year disease-free survival rate for the chemotherapy arm was raised from 42% to 50%, making it substantially different from the RT arm (50 vs. 38%, p =.007) rather than 42 percent versus 38%, which is unlikely to be meaningful. According to critics, all three randomized trials failed to establish that adjuvant chemotherapy is superior to adjuvant RT if the unadjusted progression-free survival from GOG 122 is used. The interest in integrating the modalities grew as a result of this conclusion.

Adjuvant EBRT vs Sequential EBRT and Chemotherapy

The Mario Negri Gynaecologic Oncology Group (MaNGO)/ILIADE and Nordic Society for Gynaecologic Oncology (NSGO)-9501/European Organization for Research and Treatment of Cancer (EORTC)- studies compared EBRT alone to the sequential administration of EBRT before or after chemotherapy.[78] The studies were meant to see if there was a difference in PFS, with OS as a secondary outcome. PFS was significantly improved in the sequential chemoradiation (CRT) arm compared to pelvic RT alone in the pooled analysis (HR, 0.63 [95 percent CI, 0.44- 0.89]; P =.009). There was no discernible difference between the two arms in terms of OS.

Concurrent Chemoradiotherapy

The use of a concurrent chemoradiotherapy has also been explored. Two randomized phase 3 trials compared a concurrent combination strategy to EBRT alone (PORTEC-3)[79] or chemotherapy alone (GOG 258).[80] Women with high-risk endometrial cancer were randomized to pelvic RT with or without nodal RT alone, or pelvic RT with or without nodal RT plus two doses of cisplatin (50 mg/m2) followed by four cycles of carboplatin and paclitaxel in the PORTEC-3 study.[79] There was no difference in 5-year failure-free survival (FFS) (75.5 percent vs 68.6 percent; P =.022), and no difference in 5-year overall survival (OS) (81.8 percent with CRT vs 76.7 percent with RT alone; P =.11). Maximum benefit was observed in women with stage III disease, who had a 78.7% 5-year OS and 69.3% FFS rate with CRT against 69.8% OS and 58 percent FFS with RT alone (P =.074 and P =.014, respectively) in a subgroup analysis.

Eight hundred and thirteen patients with mostly stage III and IVa disease were randomized to receive either CRT, which consisted of 2 doses of cisplatin plus volume-directed RT followed by 4 cycles of carboplatin and paclitaxel, or 6 cycles of carboplatin and paclitaxel with no RT, in GOG 258.[80] There was no difference in recurrence-free survival (HR, 0.9 [95 percent CI, 0.74-1.1]) or 5-year OS (CRT versus chemotherapy: HR, 0.9 [95 percent CI, 0.74-1.1]). (73 percent in the chemotherapy arm and 70 percent in the CRT arm).

In conclusion, adjuvant chemotherapy confers improved disease-free survival for women with stage III endometrial cancer, and also frequently utilized for any stage of serous cancer.

2.9 Recurrent disease

Early-stage patients have a good prognosis, with survival rates of 80% to 90% after five years.[68] The prognosis is bleak for people with advanced stage cancer or high-risk histologies, with 5-year survival rates of 57% for regional disease (stage III) and 19% for distant dissemination (stage IV).[81] Nonendometrioid histologies, such as uterine serous cancer and clear cell endometrial cancer, account for a large number of cancer-related deaths and recurrences, despite accounting for just 10% of all instances of endometrial cancer.[82,83]

Endometrial cancer recurrence rate is roughly 15%, with more than half of cases recurring within two years after first treatment. Patients with early-stage cancer have a recurrence rate of 2% to 15%, whereas women with advanced-stage disease or patients with aggressive histologies have a recurrence rate of up to 50%.[84] In recurrent disease, several clinicopathologic characteristics are linked to a positive prognosis. Longer disease-free intervals, low-grade and endometrioid histology, and isolated recurrence at the vaginal cuff are some of the symptoms. Recurrent endometrial cancer can manifest as a single vaginal recurrence, a pelvic recurrence, or diffuse metastatic disease in women. The course of treatment is determined by the pattern of recurrence and whether or not prior adjuvant treatment was used.

Isolated Vault Recurrence

An isolated recurrence involving the vaginal vault or cuff is referred to as a localrecurrence. It usually starts with vaginal discharge or bleeding, followed by a visible or palpable lesion on examination. Whether or not preceding radiation therapy (RT) was given determines thelikelihood of an isolated vaginal recurrence. RT is a great therapy option for women who have hadan isolated vaginal recurrence and have not had prior RT[85] In PORTEC-1, 87 percent of women who had RT for an isolated recurrence achieved a full response.[85] Vaginal recurrences within a previously irradiated region, on the other hand, have a worse prognosis. The 3-year OS rate in thispatient cohort was 43% in PORTEC-1, which was significantly lower than the 65% observed for RT-naive patients with solitary vaginal recurrences.[85] Surgical resection, re- irradiation, and pharmacological treatment with hormonal or cytotoxic drugs are all alternatives for such patients.

Locoregional recurrence

Locoregional recurrence refers to recurrent disease that occurs just in the pelvic. The role of surgery in the treatment of locoregional recurrent endometrial cancer is still debatable. For individuals with recurrence limited to the vaginal apex, surgery may entail total pelvic exenteration in an irradiated field.[86] According to a recent meta-analysis, surgical cytoreduction to no gross residual disease in individuals with recurrence or advanced disease may improve survival.[87] Although the data are less strong, radiotherapy is another option for treating large but isolated recurrences in radiotherapy-naive area.

Distant Recurrence

The goal of treatment for women who recur with distant metastases, such as bone, lung, brain, or supraclavicular nodes, is palliative. Even with advanced and recurring disease, however, 20% of patients will be cured for the long term[87]. It's vital to consider tumour-related features: histopathology, first therapy, and disease-free interval as well as recurrence pattern: distribution of disease and patient considerations: performance status and impact of management plan on quality of life to decide on treatment. Treatment options may include surgery, radiation, hormonal therapy, chemotherapy, and clinical trial participation, depending on all of these circumstances. Only a few cases of surgical treatment are successful. When a recurrence cannot be surgically removed or is generating acute symptoms, such as pain, radiotherapy is a viable treatment option. Radiotherapy can produce a quick response and improve quality of life in cases of bone metastases or vaginal haemorrhage.

Targeted therapy, in which molecular aberrations or pathways are directly inhibited, has developed as a revolutionary strategy for the innovative and effective treatment of cancers. Several cellular proliferation molecular pathways have been found, and several targets within these processes have been investigated. The mammalian target of rapamycin (mTOR), angiogenesis, and the epidermal growth factor receptor (EGFR) family have all been identified as viable therapeutic targets as our understanding of the underlying molecular biology of endometrial cancer has grown. Because systemic therapy is ineffective for patients with advanced or recurring disease, various

clinical trials have been launched to investigate targeted methods against the major drivers of these pathways.

2.10 Treatment Outcomes of endometrial cancer

Low Risk

Patients with disease restricted to the uterine corpus, histologic grade 1 or 2, endometrioid histologic subtype, and less than 50% myometrial invasion (MMI) have been characterized as low-risk endometrial cancer (EC) by several investigators.[79] Low-risk EC has a less risk of pelvic lymph node (LN) metastases (5%), as well as vaginal recurrence (1% to 3%), and has a high disease-free survival (DFS) rate of 95%.[79] The recurrence rate in women who did not receive adjuvant vaginal brachytherapy has been found to range from 4% to 7%.[79]

Intermediate Risk

In high intermediate risk endometrial cancer, vaginal recurrence accounts for more than 70% of all local recurrences. Radiation therapy (RT) reduced locoregional recurrences but had no effect on overall survival in the Gynaecologic Oncology Group (GOG)-99[66] trial and the Post-operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1[68] trial (OS). In stage I high-intermediate risk (HIR) EC, adjuvant RT was linked with a statistically significant 4.1 percent improvement in 5-year OS when compared to surgery alone, according to a recent analysis of the National Cancer Data Base (NCDB).[84]

High Risk

Endometrial tumours with a high risk histotype account for 35% of all uterine corpus cancers. Endometrial serous cancer, clear cell cancer, grade 3 or stage III endometrioid carcinoma, and de/undifferentiated carcinomas are among them. High-risk endometrial cancer patients had a 5-year survival rate of 45-70 percent.[88-90] The prognosis for women with advanced or recurring disease is poor, with a 5-year survival rate of 25-50 percent.[91]

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study Design

This was a partly descriptive and inferential retrospective cohort study review to assess outcomes of women with non-metastatic cancer of the endometrium treated at the National Centre for Radiotherapy and Nuclear Medicine with curative intent

3.2 Study Sites

The study was be conducted at the National Radiotherapy, Oncology and Nuclear Medicine Centre of Korle Bu Teaching Hospital. The NRCM was established in 1995, with collaboration from the Ghana Atomic energy Commission (GAEC), the International Atomic Energy Agency (IAEA) and the Ministry of Health of Ghana. The Centre is one of the two major government run radiotherapy centers in Ghana and receives referrals from all over the country as well as other neighbouring African countries. Approximately 1800 new cases of adult solid tumours are referred to the center every year for treatment. Services provided include radiation and medical oncology for adult solid tumours, radiotherapy for paediatric cancers, as well as haematological malignancies that require radiotherapy. A cancer registry office which collects cancer data for Greater Accra region has recently become operational.

Previously, patients were treated using 2-dimentional treatment technique which relies on bony landmarks with the aid of a simulator. Radiation was delivered using a cobalt-60 machine. In recent times, a 6MV VMAT LINAC (Figure 15) machine and a newer cobalt 60 machine have been acquired for treatment. Both 3DCRT and IMRT techniques are employed for the delivery of treatment to most cancer sites

Patients with gynaecological malignancies are referred from the Obstetrics and Gynaecology department of the same hospital and other hospitals including the Greater Accra Regional Hospital, 37 Military Hospital, Battor Catholic Hospital, Tema General Hospital and University of Ghana Hospital.

3.3 Sample Population

The study was conducted using purposive sampling method. All patients with histological confirmation of endometrial carcinoma seen at the National radiotherapy, Oncology and Nuclear Medicine Centre of Korle –Bu teaching Hospital between January 2009 and December 2018 will be included in the study. The Centre's registry logs in all patients who present with histological diagnosis of all cancers. From the registry, an average of 30 patients with histological diagnosis of endometrial cancer is seen each year in the department. End of year audits of cases however show that only about 40-50% of patients seen at the Centre follow through to have the treatments prescribed. Based on these estimates, it is therefore expected that about 120 - 150 patients will be eligible for this study. The inclusion and exclusion criteria may however reduce the numbers eligible when applied.

3.4 Inclusion Criteria

All stage I to Stage IVa histologically confirmed endometrial carcinoma patients who received definitive treatment

Patient must have had total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO)

Patients with performance status of ECOG (Eastern Corporative Oncology Group) 0-2

3.5 Exclusion Criteria

Patients with endometrial sarcoma

All women with stage IVB disease at diagnosis

Women who have been treated previously for any malignancy

Patients with recurrence at the time of referral

Patients below the age of 18 and above 85 years.

3.6 Data Collection and measurement

With approval from the hospitals institutional review board, medical records of patients with histologically confirmed endometrial cancer seen between January 2009 and December 2019 would be retrieved from National Radiotherapy, Oncology and Nuclear Medicine database. Patients were treated with curative intent comprising of total abdominal hysterectomy and bilateral salpingo-oophrectomy +/- pelvic /para-aortic lymph node sampling /dissection +/- adjuvant radiotherapy (External beam radiotherapy, EBRT / vaginal brachytherapy, VB/ EBRT +VB) +/- adjuvant Chemotherapy.

Demographic and disease-related variables- Patient's age, tribe, occupation, presenting symptoms and duration, weight, height, co – morbidities (hypertension and diabetes) histologic diagnosis, date of diagnosis, and stage were extracted from medical records.

Treatment-related variables-Surgery (Type and date of surgery, lymphadenectomy, number of lymph nodes) External beam RT details (date of start/end, dose, number of fractions, technique), brachytherapy (date of start/end, dose, number of fractions, technique) and chemotherapy details (number of cycles, dose at each cycle, date of delivery of each cycle) were obtained from the patient's medical record.

Data extraction was done primarily by the researcher, however, any assistance where needed was sought from junior colleagues and departmental records staff.

All patients who received treatment were intended for follow up every three months for the first year post treatment and 6 monthly thereafter. At five years, patients were followed up yearly. Local, regional or distance recurrence was recorded from patient's medical records. Where patients were not followed up at the National Radiotherapy, Oncology and Nuclear medicine Centre (NRONMC), patients were called via telephone to ascertain their status and to ask about recurrence if followed up by a gynaecologist. Patients were then encouraged to report to NRONMC for clinical assessment.

For patients whose record of death was unavailable in their medical records, a call to the next of kin was made and date and cause of death determined.

Patients were then risk stratified according to the PORTEC risk stratification system

1) Low risk (Endometrial adenocarcinoma stage Ia, grade 1)
2) Intermediate risk (Endometrial adenocarcinoma with any of the following: Grade 1 histology and myometrial invasion of ≥ 50% or Grade 2 histology with any myometrial invasion or Grade 3 histology with myometrial invasion < 50%)
3) High intermediate risk (Age > 60 years with grade 1 or 2 histology and myometrial invasion >50% , age > 60 with grade 3 histology and myometrial invasion <50%)
4) High risk (Stage III–IV disease or uterine serous carcinoma or clear cell carcinoma of any stage) according to the PORTEC definition to determine disease-free, 2 and 5 year overall survival, as well as recurrence rates and factors affecting recurrence for the various risk groups.

Definition of End Points from start of treatment

Overall survival rate - The proportion of patients in the study who are alive as at December 2020. This was calculated from the date of histopathologic diagnosis to survival status (dead or alive) of the patient as at the end point.

Disease-free survival rate- The proportion of patients who survived without any signs or symptoms of disease as at December 2020.This was calculated from the date of completion of treatment to the date of first diagnosis of disease recurrence or date of last visit to the clinic in patients who were disease-free.

Locoregional recurrence rate- Is defined as the proportion of patients with re-appearance or recurrence of cancer of the same histology in the vagina or pelvic region after a disease- free period as at December 2020.

Distant recurrence rate- Is defined as the proportion of patients with recurrence of cancer outside the pelvic region and usually involving another organ within the body after a disease-free period as at December 2020.

Recurrences will be analyzed according to first site of recurrence as well as the total number of recurrences

Simultaneous vaginal and pelvic recurrence were be considered pelvic recurrence.

Simultaneous vaginal, pelvic, and distant recurrence were considered distant recurrence.

Abdominal recurrences outside the pelvic area (peritoneal carcinomatosis, liver, lung and para-aortic lymph nodal metastases) were considered distant metastases.

3.7 Data management and Analysis

Demographic, tumour and treatment factors were input in an excel document from where descriptive statistics were outlined using tables and graphs. Depending on the type of data, appropriate descriptive statistics, measures of location (such as mean or median) and measures of spread (such as standard deviation, range or interquartile range) were used. Kaplan-Meier curves were developed to determine the survival function for each group. Patients with missing or incomplete information on survival were censored in order to carry out full actuarial survival analysis. Log-rank test was used to compare survival outcomes of various groups. Cox regression was used to determine the factors associated with endometrial cancer recurrence and survival and the confidence level was set at 95%. P- value of ≤ 0.05 was considered significant for all statistical test in the study. Statistical package used for analysis was SPSS software version 20.

3.8 Ethical/ Legal Consideration

Ethical approval for the study was obtained from the Korle Bu Teaching Hospital Institutional Review Board (KBTH-IRB). Data was retrieved from the medical records of patients, excluding the need for informed consent. This study involved retrieval of folders with no direct contact with patients because of the retrospective nature of study. This posed very little ethical challenge. As the principal investigator and a practitioner in the unit, I had direct access to patient's records. Possible damage to patient's record was very minimal. Patients' right to confidentiality and anonymity were ensured. Physical data from the patients' records was stored electronically on

the principal investigators computer securely and was only to be accessible to the research team. The data will be stored for a maximum of five years to allow for future publication and reference where necessary. Approval for access to patient's records was granted by the head of department.

CHAPTER FOUR

4.0 Results

4.1 Demographic Characteristics

Two hundred and sixty –nine (269) patients with the diagnosis of endometrial cancer were seen at the gynaecology oncology clinic between the periods of 1st January 2009 and 31st December 2018. 146 patients met the inclusion criteria which included all stage I to stage IVa histologically confirmed endometrial carcinoma patients who received definitive treatment. Patient must have had total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) and a performance status of ECOG (Eastern Corporative Oncology Group) 0-2.

One hundred twenty-three (45.7%) were excluded from the study. This included patients with endometrial sarcoma (7.7%), carcinosarcoma (11%) and all women with distant metastasis at presentation (26.7%). There were no patients who had been treated for any malignancy in the past and none was below the age of 18 and above 85 years.

The mean age was 61.3 years (Std dev 9.0, Range 33-83 year)) (Table 4). Peak age group was 60 to 69 years and 10% were below the age of 50 years. One hundred and twelve (77%) women were post - menopausal while 15 (10%) were pre – menopausal (Figure 5). Of the 146 patients, 93(64%) were married and a significant proportion of respondents (77%) had received formal education of which the majority was secondary education (49, 34%). More than half (77, 53%) of these w omen worked in the informal sector of sales and services and majority were Christian, 91% (133). (Table 3).

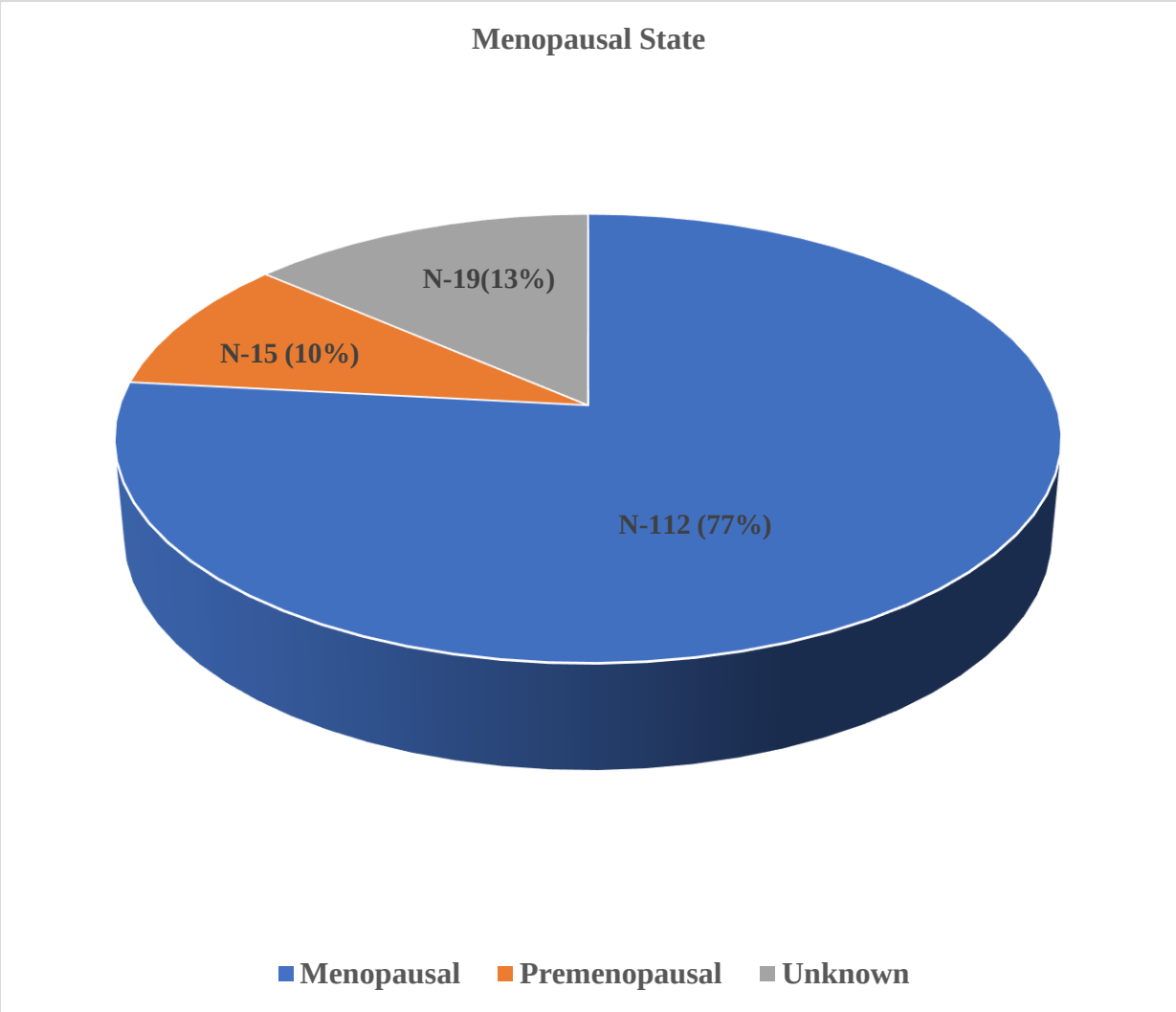
Table 3: Summary description of sociodemographic characteristics

Demographics	Groups	Number	Percentage
Age	<50	18	13%
	50-59	40	27%
	60-69	66	45%
	≥70	22	15%
Marital Status	Single	19	13%
	Married	94	65%
	Divorced	18	12%
	Widowed	15	10%
Educational Level	Basic	33	23%
	Secondary	49	33%
	Tertiary	32	22%
	None	32	22%
Occupation	Formal	37	25%
	Informal	87	59%
	Unemployed	23	16%
Religion	Christian	134	91%
	Muslim	12	9%

Table 4: Statistical Analysis of Age

Age	
Mean	61.3
Median	61
Mode	57
Standard Deviation	9
Range	50
Minimum	33
Maximum	83
Count	146

Figure 5: Distribution of Premenopausal and Post-Menopausal women



4.2 Risk Factors

The following risk factors were assessed in the sample population. Age at menarche, age at menopause, Body Mass Index (BMI), prevalence of Hypertension and diabetes. The mean age at menarche was 15.2 years (std dev 1.8) while that of menopause was 50 years (std dev.3.5) (Table 5).

The life time number of year of menstruation (LNYM) represented the cumulative duration of menstrual cycles in a woman's lifetime. This was calculated as the total number of years between age at menarche to age at menopause (Not adjusted for number of full-term pregnancies, abortions or miscarriages). The LNYM was 35.2 years (std dev 4.1) with a range of 20 to 40 years. The mean and median number of live births was 3 with a range of 1 to 11. Nulliparity was 8.6% among the study population.

Mean BMI was 28.2mg/m^2 (std dev 6.1) (Table 5). Majority of patients, (98, 67%) were above normal BMI with 35% being obese (Table 6). Two patients were wheel chair bound and weight could not be assessed.

Prevalence of hypertension and diabetes within the group was 57% and 20% respectively (Figure 6 &7).

Table 5: Descriptive Summary of Menarche, Menopause, LNYM and BMI

	Menarche	Menopause	LNYM	Parity	BMI (kg/m^2)
Mean	15.2	50.4	35.2	3	28.2
Median	15.0	50.0	36.0	3	27.8
Mode	15.0	50.0	38.0	3	30.1
Standard Deviation	1.8	3.5	4.1	2	6.2
Minimum	11.0	35.0	20.0	0	16.2
Maximum	21.0	59.0	45.0	11	50.8
Count	115	112	74	124	114

LNYM- Lifetime number of years of menstruation

BMI- Body mass index

Table 6: Body Mass Index Distribution

BMI (Kg/m$^{2)}$	**Frequency**	**Percentage**
Underweight **<18.5**	5	3%
Normal **18.5-24.9**	52	29%
Overweight **29-29.9**	56	32%
Obese **>30.0**	61	35%
Total	142	99%

Figure 6: Prevalence of Hypertension

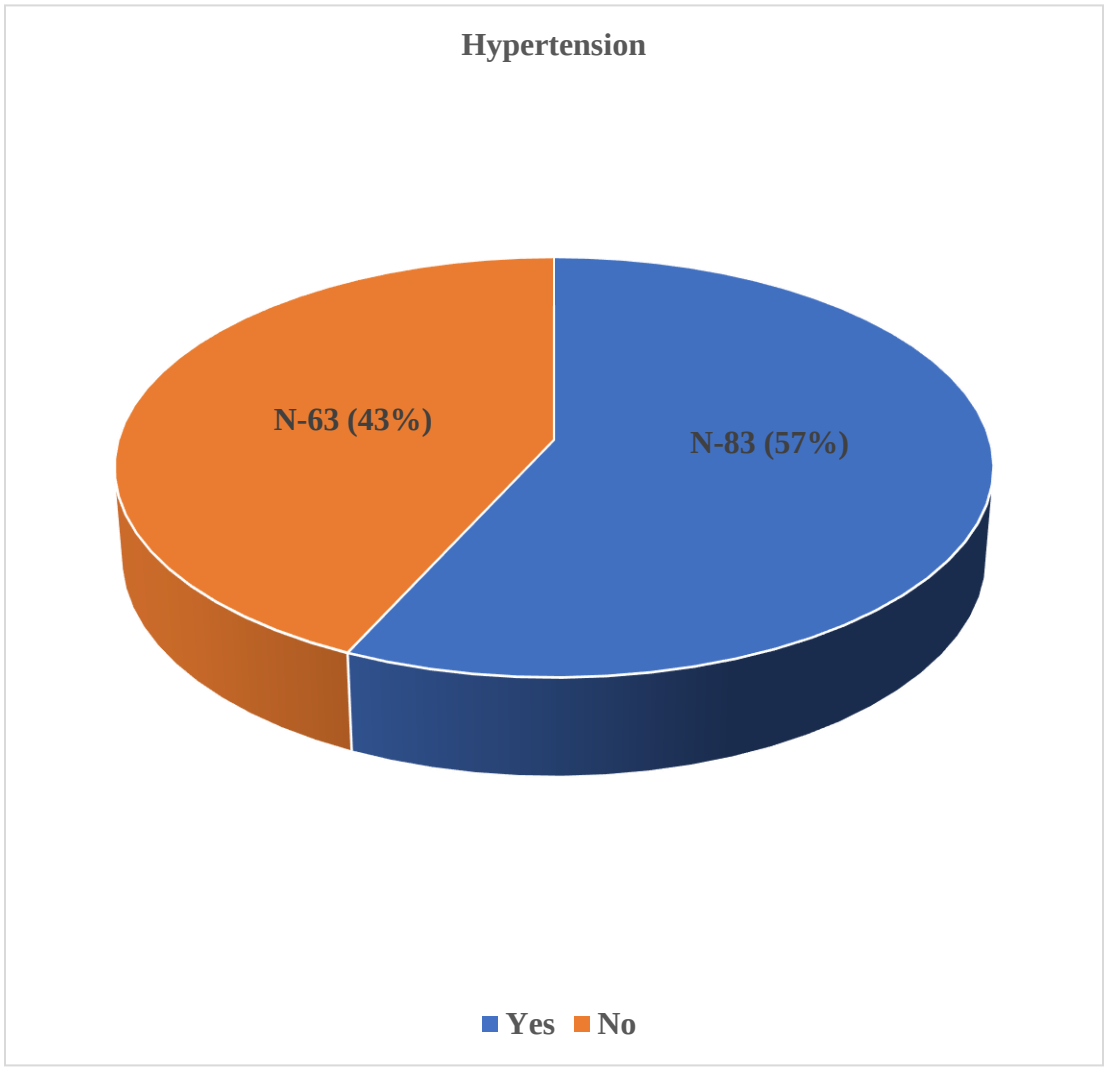
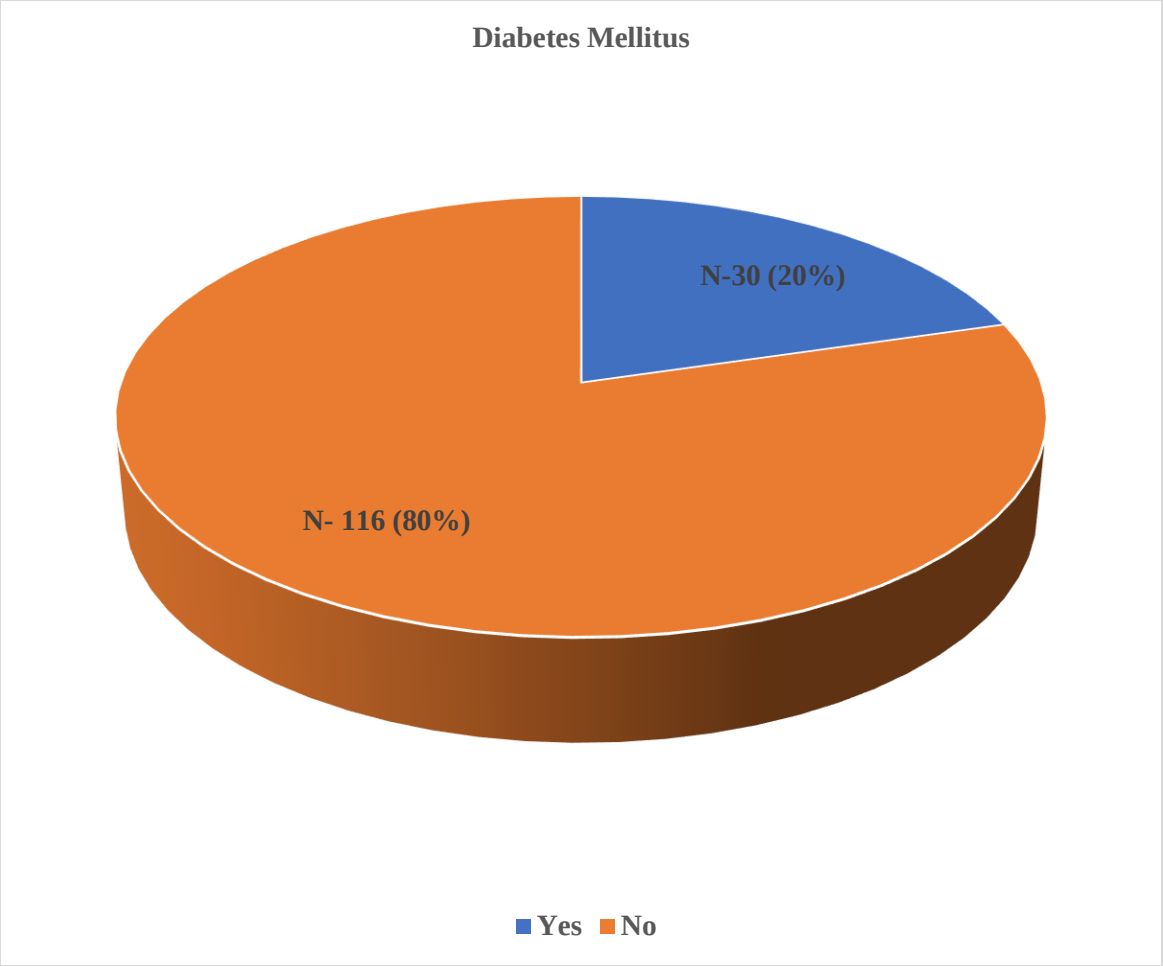


Figure 7: Prevalence of Diabetes Mellitus



4.3 Clinicopathological Features

Abnormal vaginal bleeding was the commonest presenting symptom accounting for 78.9% of all presentations. This comprised of post - menopausal bleeding (72.7%), menorrhagia (5.1%) and intermenstrual bleeding (1.1%). Vaginal discharge accounted for 6.8%. (Table 7). Most women (54%) reported to the health facility less than six months after the initial symptom. A significant number (28, 15.9%) however delayed for over 12 months. (Figure 8)

Endometrioid adenocarcinoma was the major histological type (79.5%), followed by papillary adenocarcinoma (11%), papillary serous adenocarcinoma (6.7%), clear cell adenocarcinoma (1.4%) and undifferentiated carcinoma (1.4%) (Table 8).

All patients were staged using the FIGO 2009 staging system. Based on this, less than half of the patients had stage 1 disease (79,47%). Stage 2, 3 and 4 were 30%, 21% and 2% respectively (Figure 9).

Using the PORTEC definition, patients were assigned to various risk groups (Figure 10). These were

1) Low risk (Endometrioid adenocarcinoma stage 1 and grade 1) accounting for 6.2% of the total sample size.

2) Intermediate risk (Endometrial adenocarcinoma with any of the following: Grade 1 histology and myometrial invasion of ≥ 50% or Grade 2 histology with any myometrial invasion or Grade 3 histology with myometrial invasion < 50%) accounting for 30.1%.

3) High - intermediate risk (Age > 60 years with grade 1 or 2 histology and myometrial invasion >50%, age > 60 with grade 3 histology and myometrial invasion <50%) accounting for 33.6%.

4) High risk (Stage III–IV disease or uterine serous carcinoma or clear cell carcinoma of any stage) accounting for 30.1%.

Table 7: Clinical Presentation

Presentation	Frequency	Percentage (%)
Abdominal distension	2	1.7%
Abdominal mass	3	2.3%
Abdominal pain	10	6.8%
Amenorrhea	1	0.6%
Irregular menstrual period	2	1.1%
Menorrhagia	7	5.1%
Postmenopausal bleeding	107	72.7%
Urinary incontinence	1	0.6%
Vaginal discharge	13	9.1%
Total	146	100%

Figure 8: Duration of Presenting Symptom

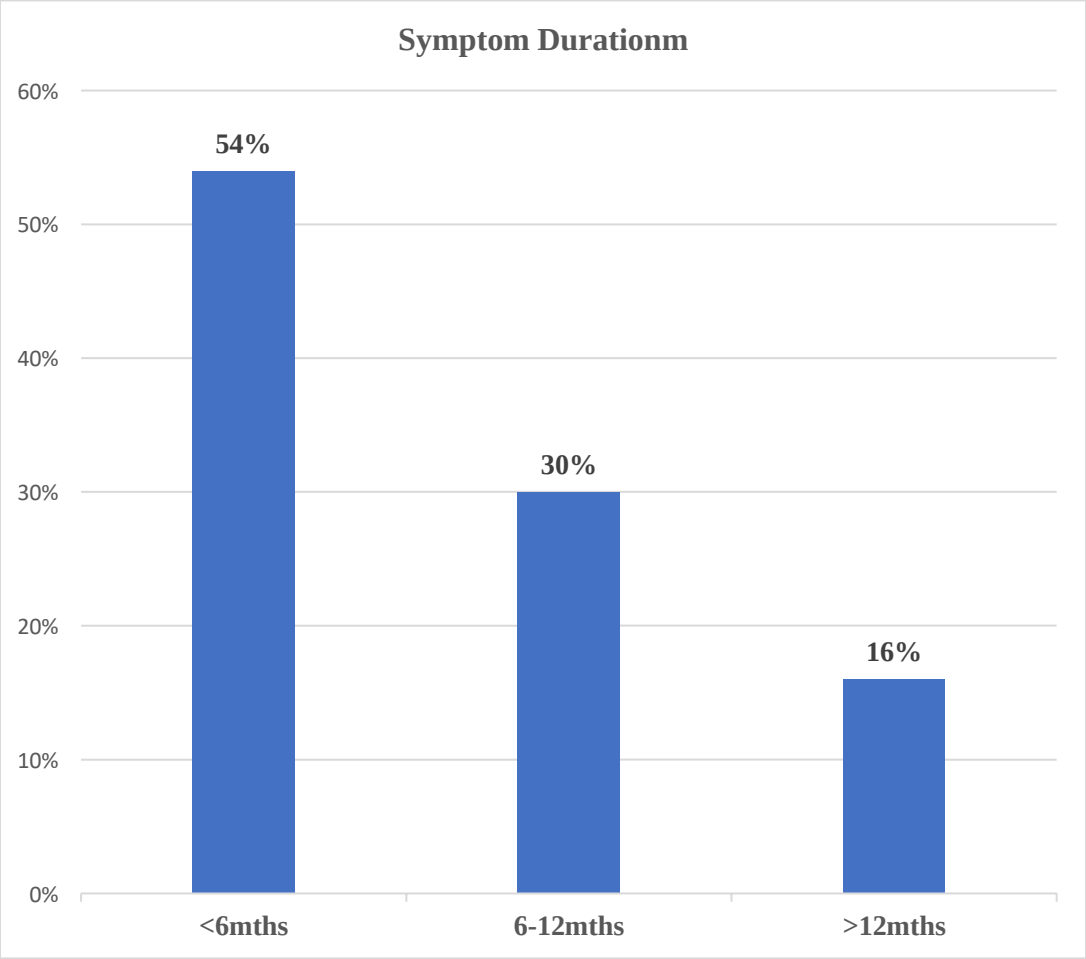


Table 8: Histological Types

Histological Type	Frequency	Percentage
Endometrioid adenocarcinoma	116	79.5%
Papillary adenocarcinoma	16	11%
Papillary Serous adenocarcinoma	10	6.7%
Clear Cell Carcinoma	2	1.4%
Undifferentiated carcinoma	2	1.4%
Total	146	100%

Figure 9: Stage Distribution

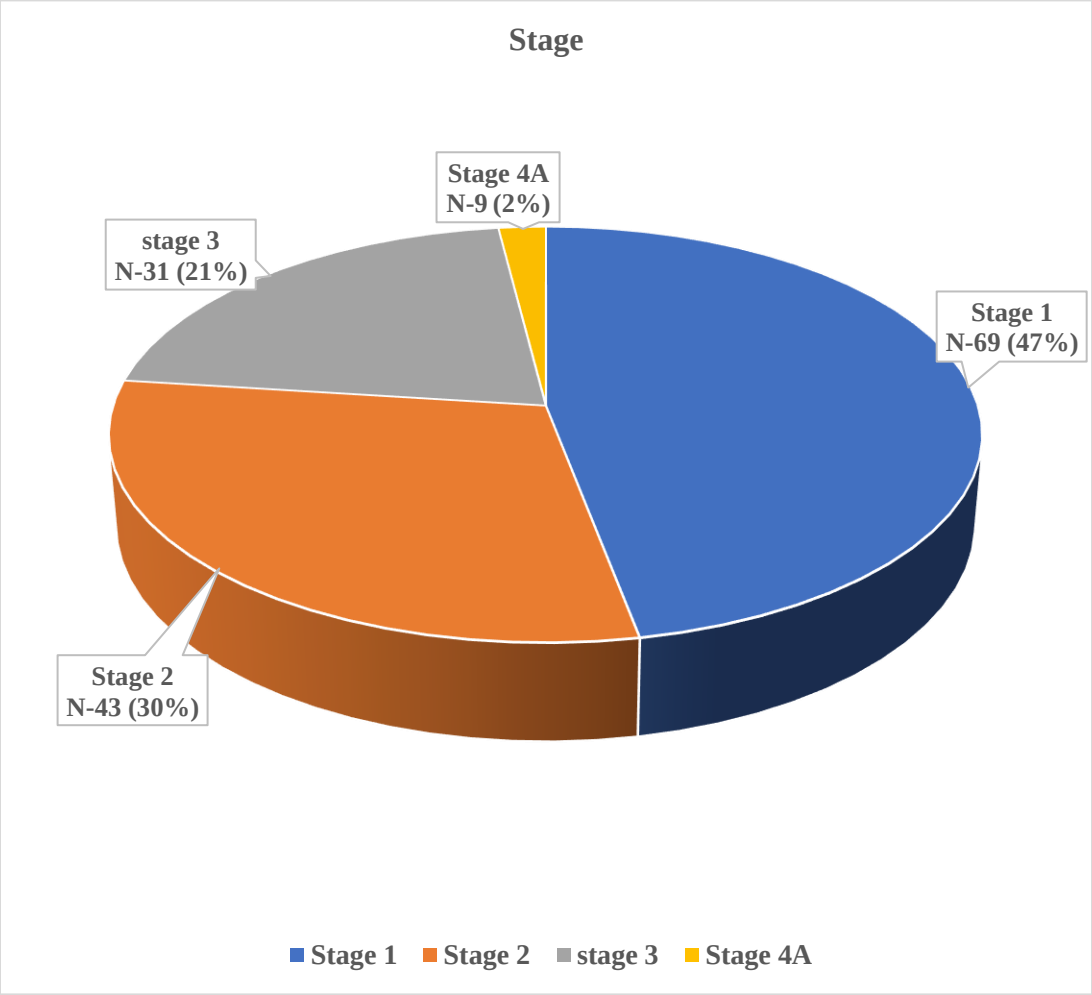


Figure 10: Risk Stratification

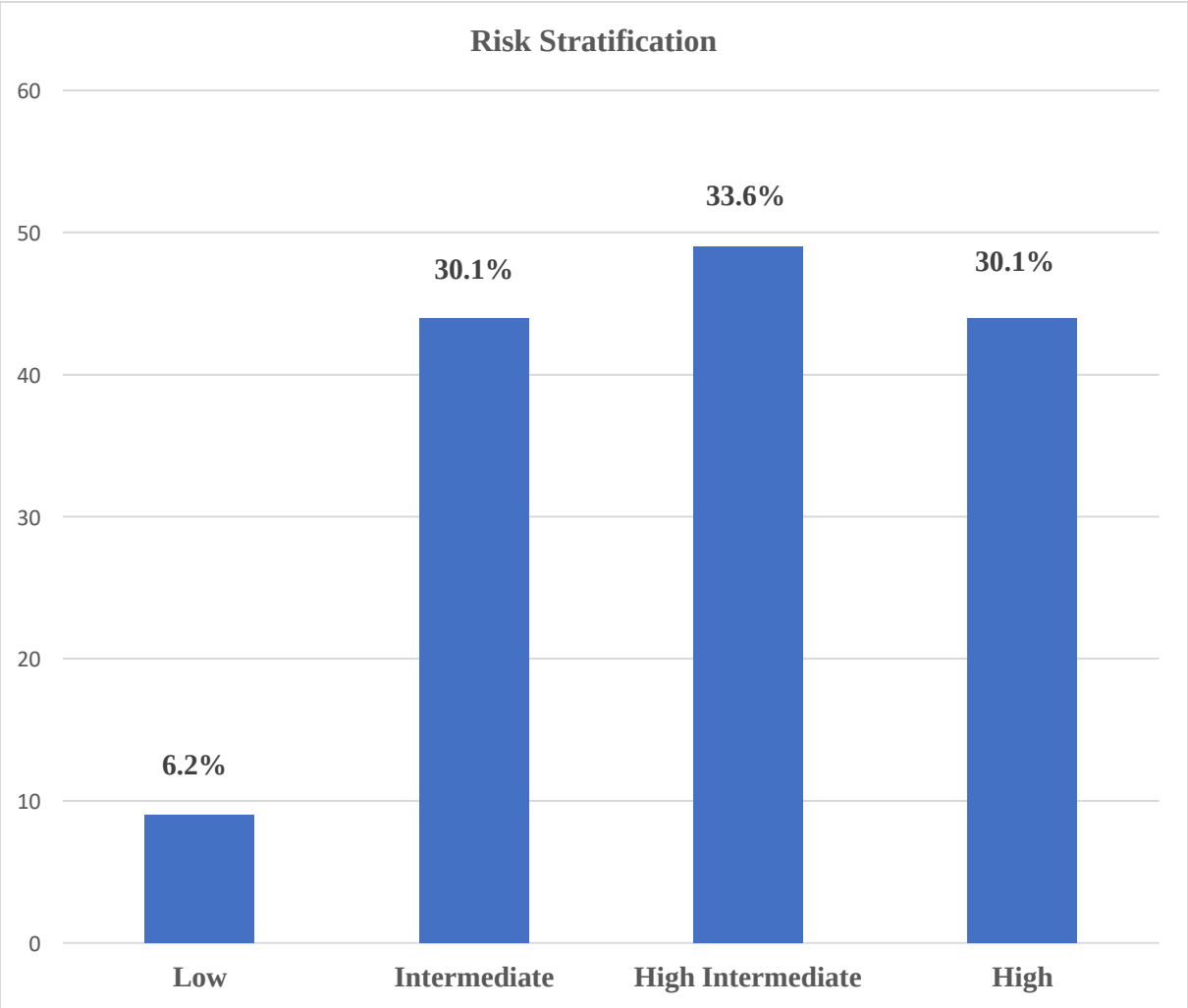


Table 9: Clinicopathological features in different Risk Groups

Clinicopathological Feature		Risk Stratification				Total
		Low	Intermediate	High Intermediate	High	
Age	≤60	4	39	5	15	**63**
	>60	5	5	44	29	**83**
	Total	**9**	**44**	**49**	**44**	**146**
Stage	1a	9	7	3	1	**20**
	1b	-	29	30	-	**59**
	2	-	8	16	5	**29**
	3	-	-	-	35	**35**
	4	-	-	-	3	**3**
	Total	**9**	**44**	**49**	**44**	**146**
Grade	1	9	15	10	5	**36**
	2	-	26	21	19	**66**
	3	-	1	14	13	**28**
	Not Stated	-	2	4	7	**13**
	Total	**9**	**44**	**49**	**44**	**146**
Histology Type	Clear Cell Carcinoma				2	**2**

	Endometrioid adenocarcinoma	7	36	43	30	**116**
	Neuroendocrine carcinoma				1	**1**
	Papillary adenocarcinoma	2	8	6		**16**
	Serous Papillary Carcinoma				10	**10**
	Undifferentiated Carcinoma				1	**1**
	Total	**9**	**44**	**49**	**44**	**146**

4.4 Treatment

Surgery

All patients included in the study had total abdominal hysterectomy and bilateral salpingo – oophrectomy.

Sixteen had pelvic +/- para-artic sampling during surgery giving a lymph node dissection rate of 11% (Figure 11). The pelvic lymph nodes dissected included common iliac, internal and external iliac and obturator group of lymph nodes. The average number of pelvic and para-aortic lymph nodes sampled were 19 (Range 4-44) and 6 (Range 3-9) respectively (Table 10). The lymph node positivity rate was 62.5%.

Adjuvant Therapy

Fifty-four patients (36.9%) in total received adjuvant therapy (Figure 12). The choice of adjuvant therapy was based on the risk stratification and choice of attending physician. Adjuvant therapy included external beam radiotherapy (EBRT) to the pelvis +/- vaginal brachythera py +/ - chemotherapy (Figure 13).

External Beam Radiotherapy

EBRT was delivered with a cobalt -60 teletherapy machine (Figure 14) using 2-dimensional treatment technique with either two parallel opposing fields (AP/PA) or four fields (AP/PA and two lateral fields) (Figure 15). Radiation dose delivered was between 45 Gy-50.4 Gy at 1.8 Gray per fraction over a period of 5-6 weeks.

Vaginal Brachytherapy

Vaginal brachytherapy was delivered either with Low-dose rate in 19 patients until July2014 and high-dose rate in 17 patients thereafter with a dose of 50Gy using tandem and ovoid applicator or 5Gy by 3 fractions using cylinder applicator respectively prescribed to vaginal depth of 0.5cm. (Figure 16)

Chemotherapy

Adjuvant chemotherapy received by high risk group included IV Carboplatin (AUC -5) and Paclitaxel 175mg/m2 given three weekly for six cycles or IV Cisplatin 50mg/m2 and Adriamycin 60mg/m2 given three weekly for 6 cycles.

Figure 11: Surgical Intervention

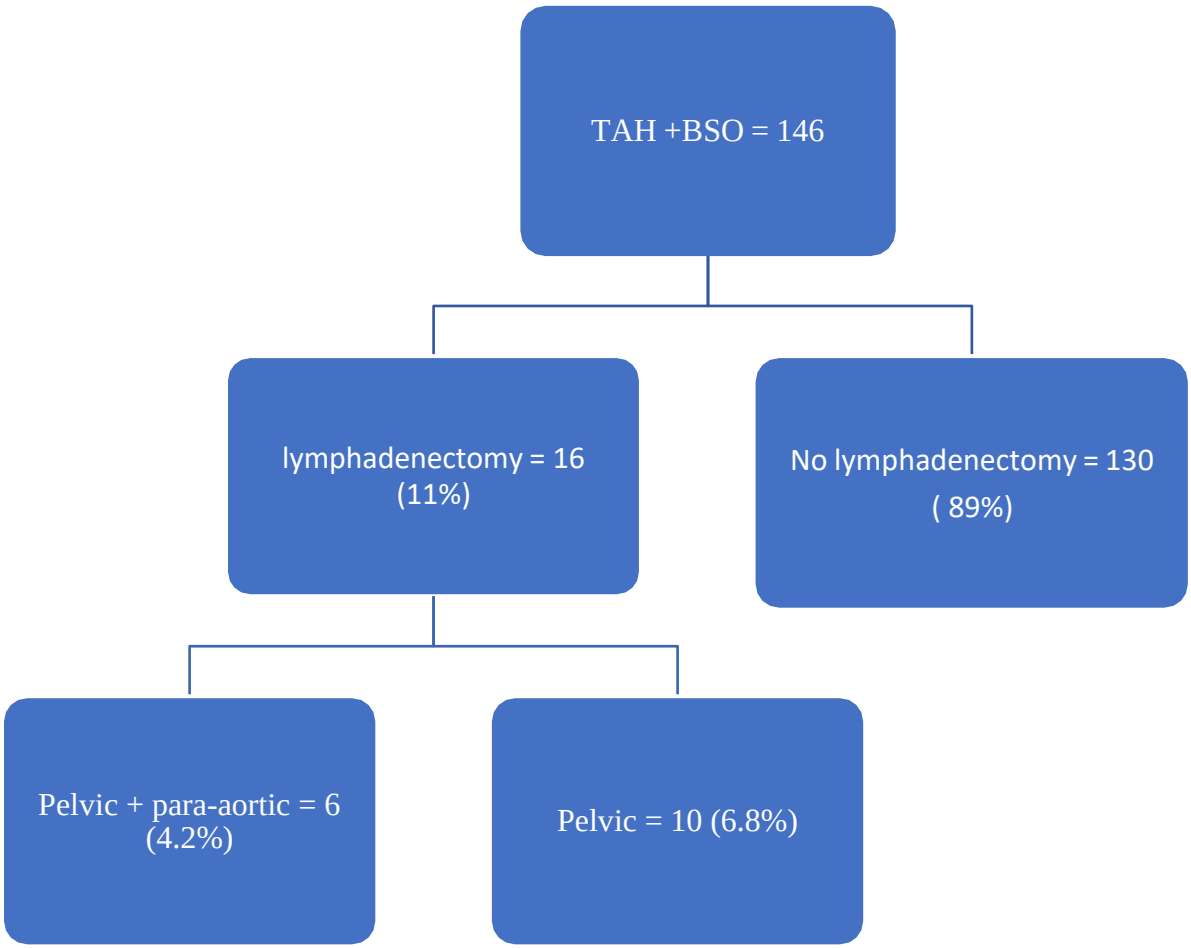


Table 10: Statistical analysis of lymph node dissection

Parameter	Pelvic	Para Aortic
Mean	19.6	6.6
SD	13.7	2.6
Median	18.5	7
Range	4 – 44	3 – 9

Figure 12: Treatment Received

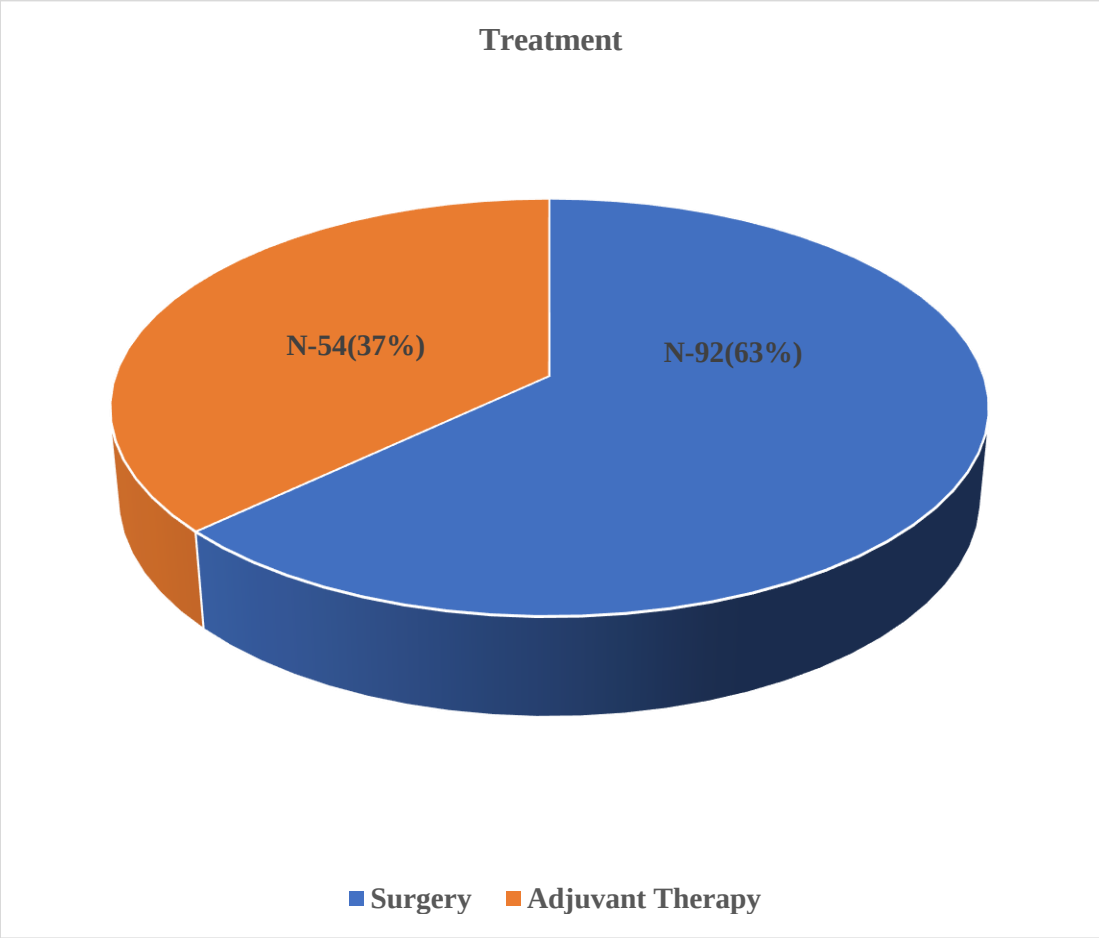


Figure 13: Treatment Received per risk group

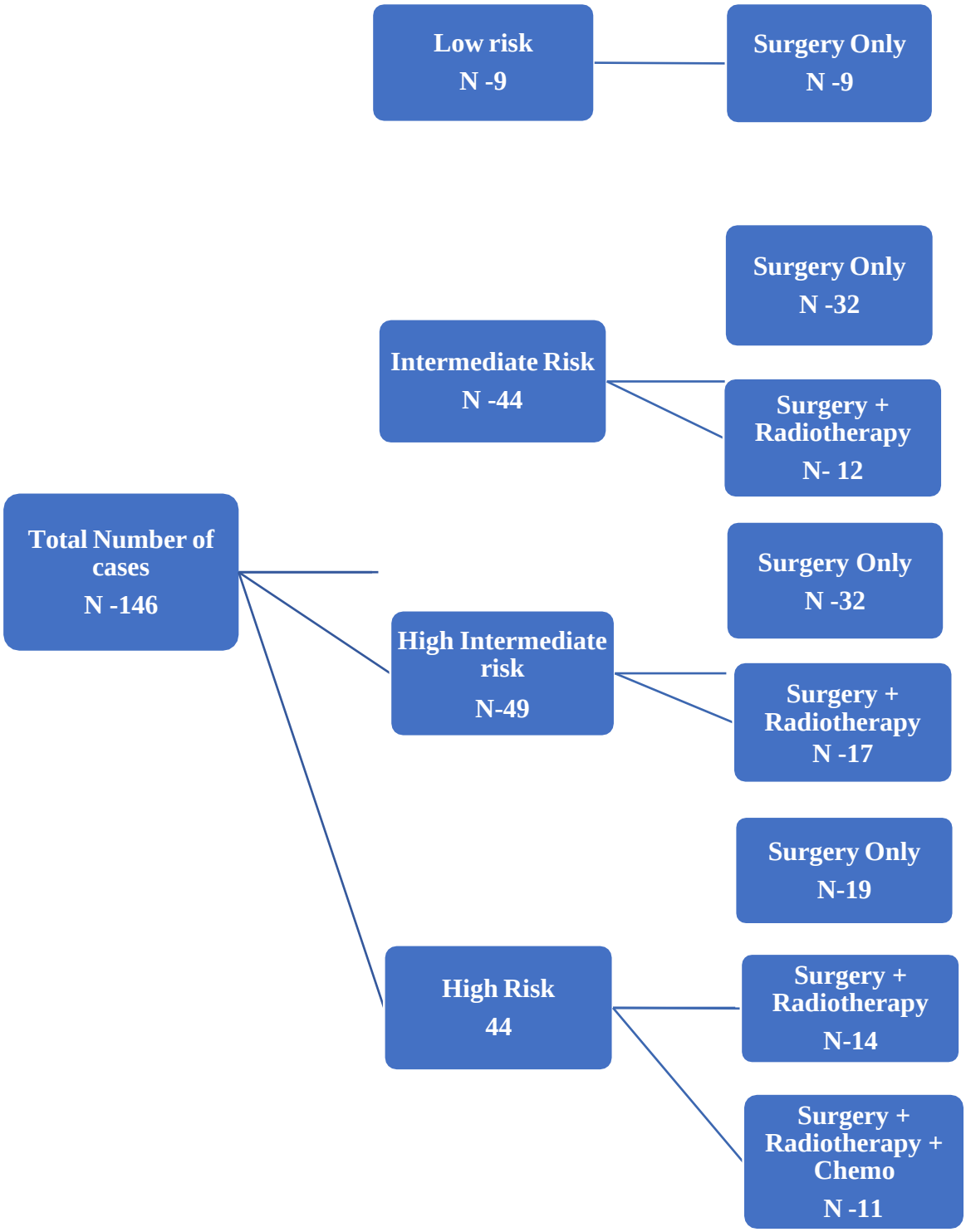


Figure 14: Cobalt 60 Teletherapy Machine

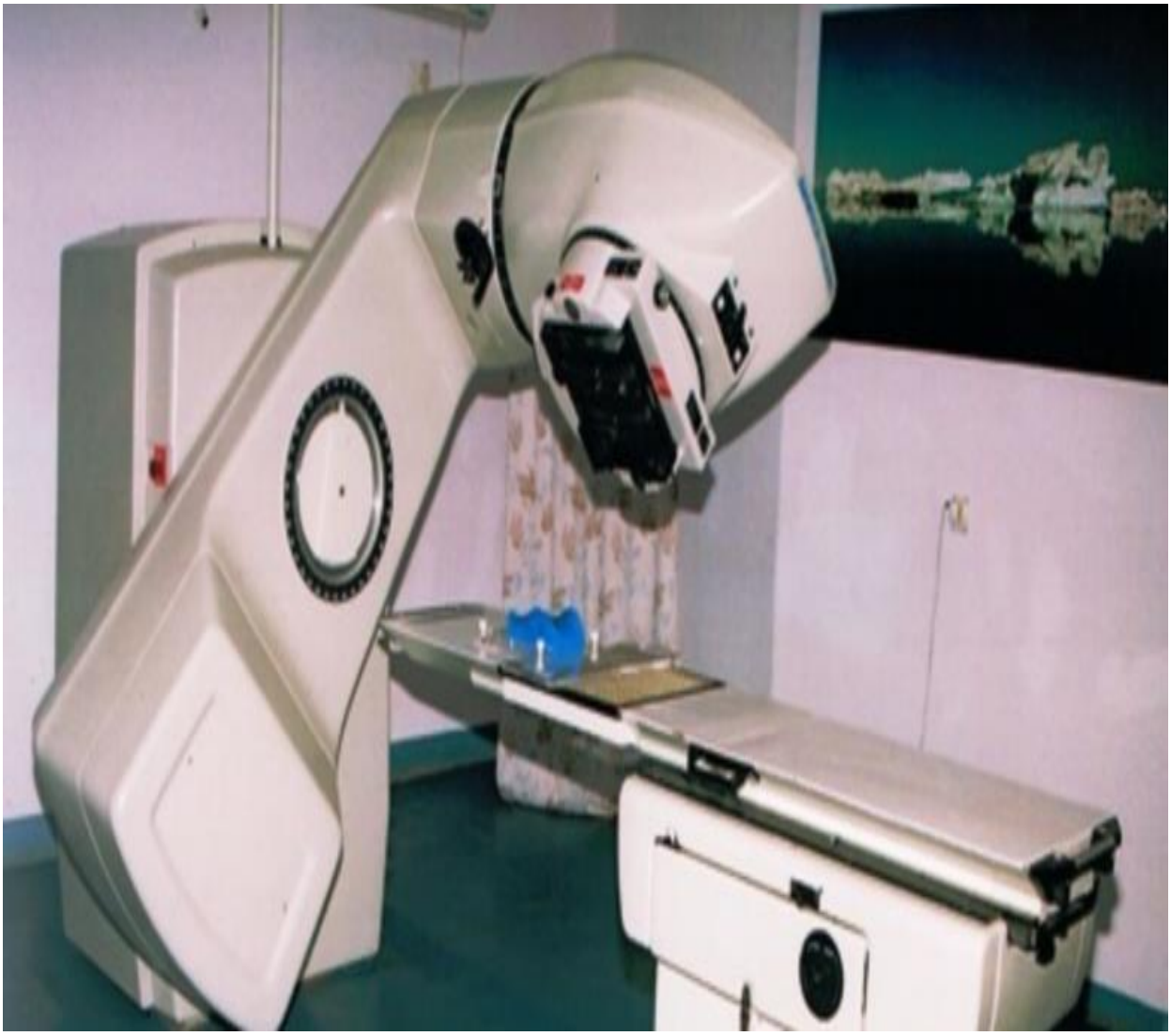


Figure 15: Brachytherapy applicators

Figure 15A: Cylinder Applicator

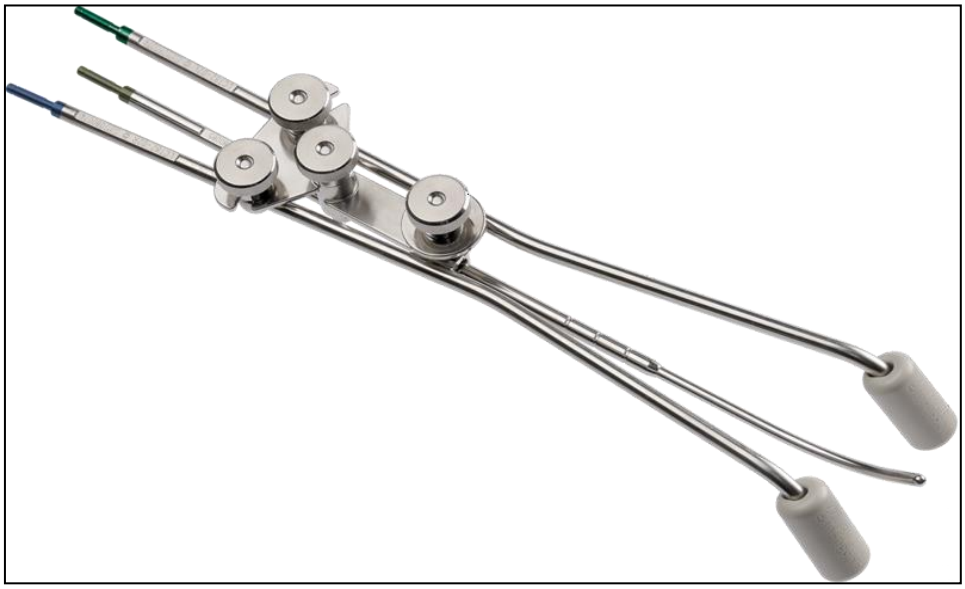
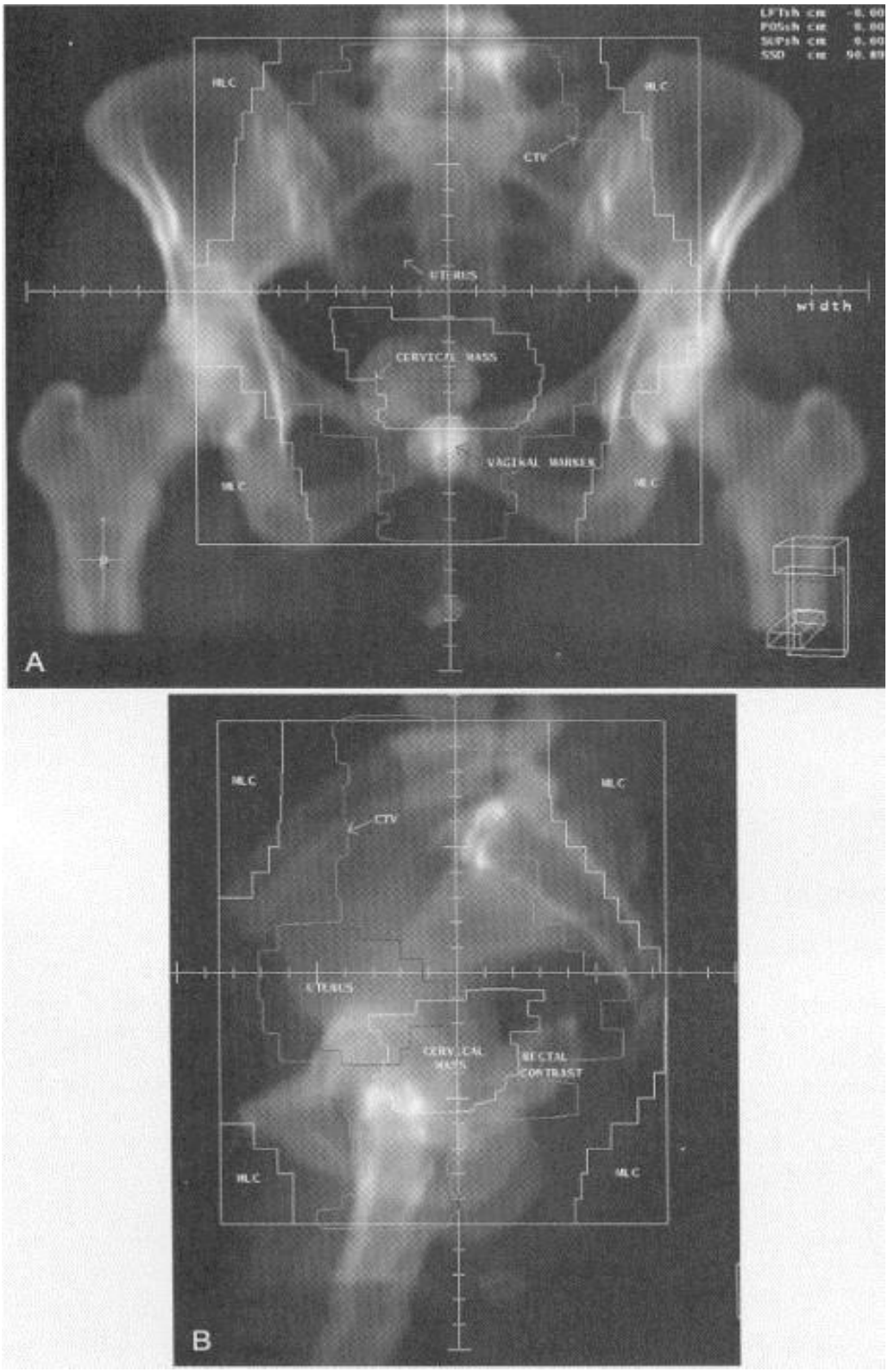


Figure 15B: Tandem and ovoid applicator

Figure 16: Conformal radiotherapy treatment field



4.5 Overall and Disease-free survival rates based on stratification

The median follow up was for the entire study population was 34.5 months (Range: 1-148 months).

The Overall survival was calculated from the date of histopathologic diagnosis to the survival status as at December 2020 or if deceased, to the date of death. This included patients who had salvage treatment after recurrence.

Disease-free survival was calculated from the date of completion of treatment to the date of first diagnosis of disease recurrence or date of last visit to the clinic in patients who had not developed recurrence as at the end point of this study or date of death for patients who had died without any evidence of recurrence**.**

The 2 year overall survival for low, intermediate, high – intermediate and high risk was 100%, 79%, 80.5% and 58% whiles 5 year OS was 87.5%, 69%, 57% and 30.5% respectively, which was statistically significant (P value - 0.001) (Table 11). There was however no statistically significant difference in disease-free survival at both 2 and 5 years for the various risk stratification groups (Table 11).

The use of adjuvant radiotherapy compared to surgery alone led to a statistically significant improvement in 2 and 5year DFS for intermediate risk 100% vs 54% and 100% vs 46% and high-intermediate risk 87.5% vs 63% and 87.5% vs 52% respectively (P value -0.006). There was however no statistically significant overall survival benefit for the use of adjuvant radiotherapy in these two groups. (Table 12)

With respect to the high risk group, the use of adjuvant therapy (radiotherapy +/ - chemotherapy) resulted in a statistically significant benefit in 2 and 5 year DFS but no statistically significant overall survival benefit. (Table 12).

Kaplan-Meier survival analysis was run to compare DSF and OS of patients who had lymphadenectomy verses those who did not. Although 5 year DFS was better in patients who had lymphadenectomy (81% vs 58%), it was not significant (p-value: 0.18). Overall survival was not significantly different between the two group (Figure 25 &26).

Below are overall and disease-free survival curves for the whole sample population according to risk groups (Figure 24 & 25) as well as survival curves for various risk groups according to treatment received (Figure 17 -24).

Table 11: Overall and Disease-Free Survival rates for various risk groups from Kaplan-Meier curves

Overall survival	**2year (%)**	**5year (%)**	**(Log Rank (Mantel-Cox) p-value**
Low Risk	100	87.5	**0.001**
Intermediate Risk	79.0	69.0	
High-Intermediate Risk	80.5	57.0	
High Risk	58.0	30.5	
Disease-free survival			**0.747**
Low Risk	67.0	67.0	
Intermediate Risk	66.0	59.0	
High-Intermediate Risk	72	64.5	
High Risk	63.0	54.0	

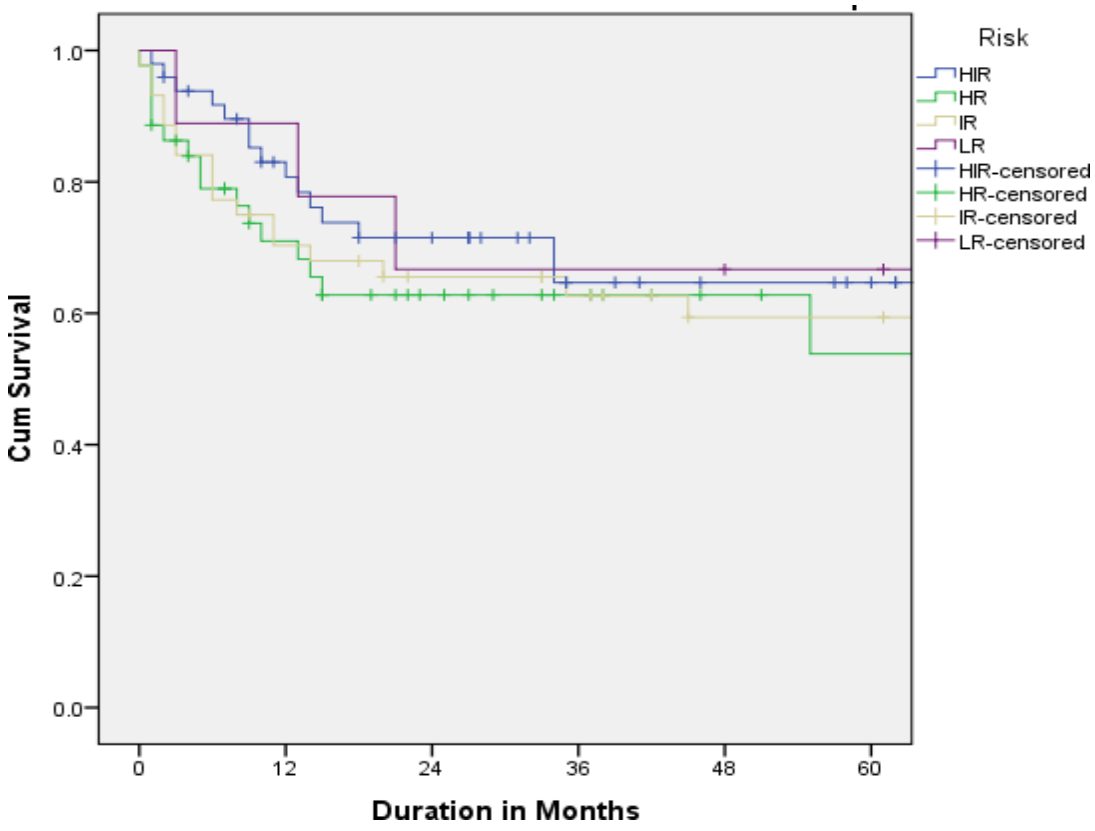
Table 12: Overall and Disease-free survival rates for various risk groups from Kaplan-Meier curves with respects to treatment received

Risk Groups	Survival	Treatment	2 year (%)	5 year (%)	p-value
Intermediate Risk	DFS	Surgery	54.0	46.0	**0.006**
		Surgery+ Radiotherapy	100	100	
	OS	Surgery	75.0	64.5	**0.174**
		Surgery+ Radiotherapy	91.0	82.0	
High Intermediate Risk	DFS	Surgery	63.0	52.0	**0.041**
		Surgery+ Radiotherapy	87.5	87.5	
	OS	Surgery	72.0	37.5	**0.087**
		Surgery+ Radiotherapy	92.0	88.0	
High Risk	DFS	Surgery	45.5	0.0	**0.041**
		Surgery + Radiotherapy +/-Chemotherapy	70.5	70.5	
	OS	Surgery	47.5	19.0	**0.138**
		Surgery + Radiotherapy +/- Chemotherapy	67.0	38.0	

Table 13: Case processing summary for DFS analysis of whole study population

Risk	Total N	N of Events	Censored	
			N	Percent
HIR	49	15	34	69.4%
HR	44	16	28	63.6%
IR	44	17	27	61.4%
LR	9	3	6	66.7%
Overall	146	51	95	65.1%

Figure 17: Kaplan-Meier Disease-Free Survival curve for risk groups

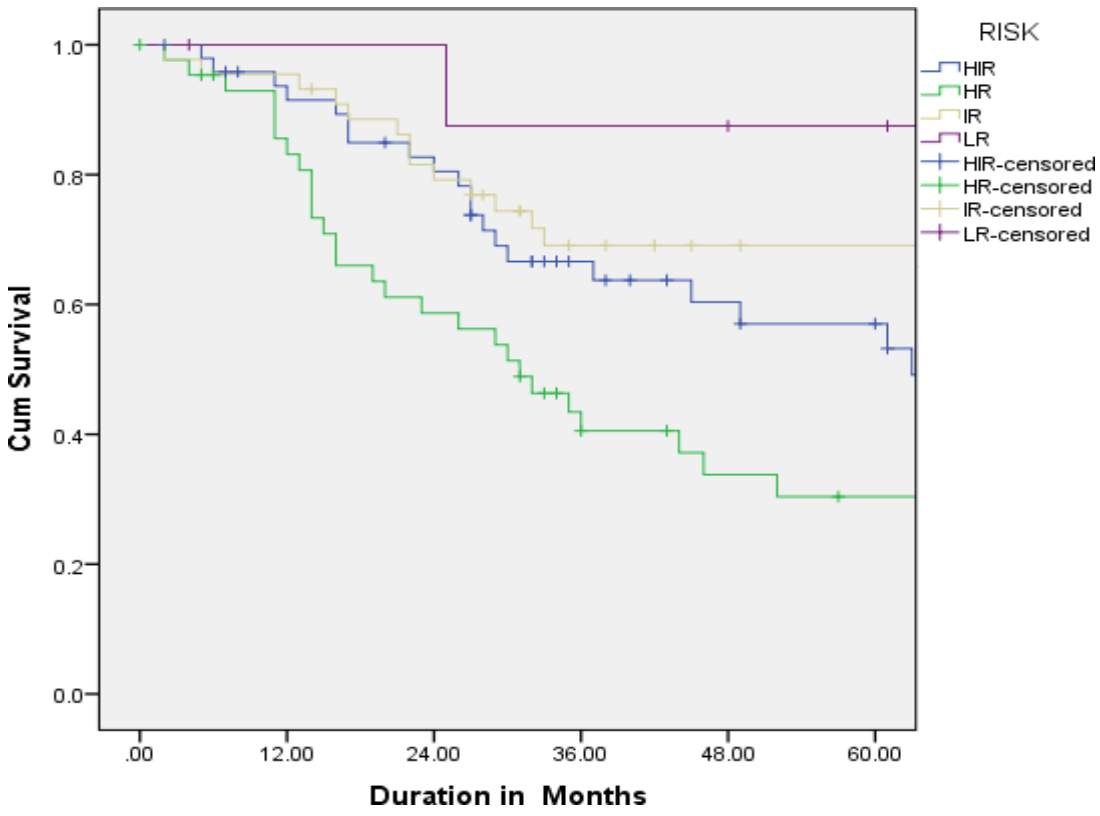


P value: 0.747

Table 14: Case processing summary for OS analysis of whole study population

RISK	Total N	N of Events	Censored	
			N	Percent
HIR	49	22	27	55.1%
HR	44	29	15	34.1%
IR	44	15	29	65.9%
LR	9	2	7	77.8%
Overall	146	68	78	53.4%

Figure 18 : Kaplan-Meier Overall Survival curve for risk groups

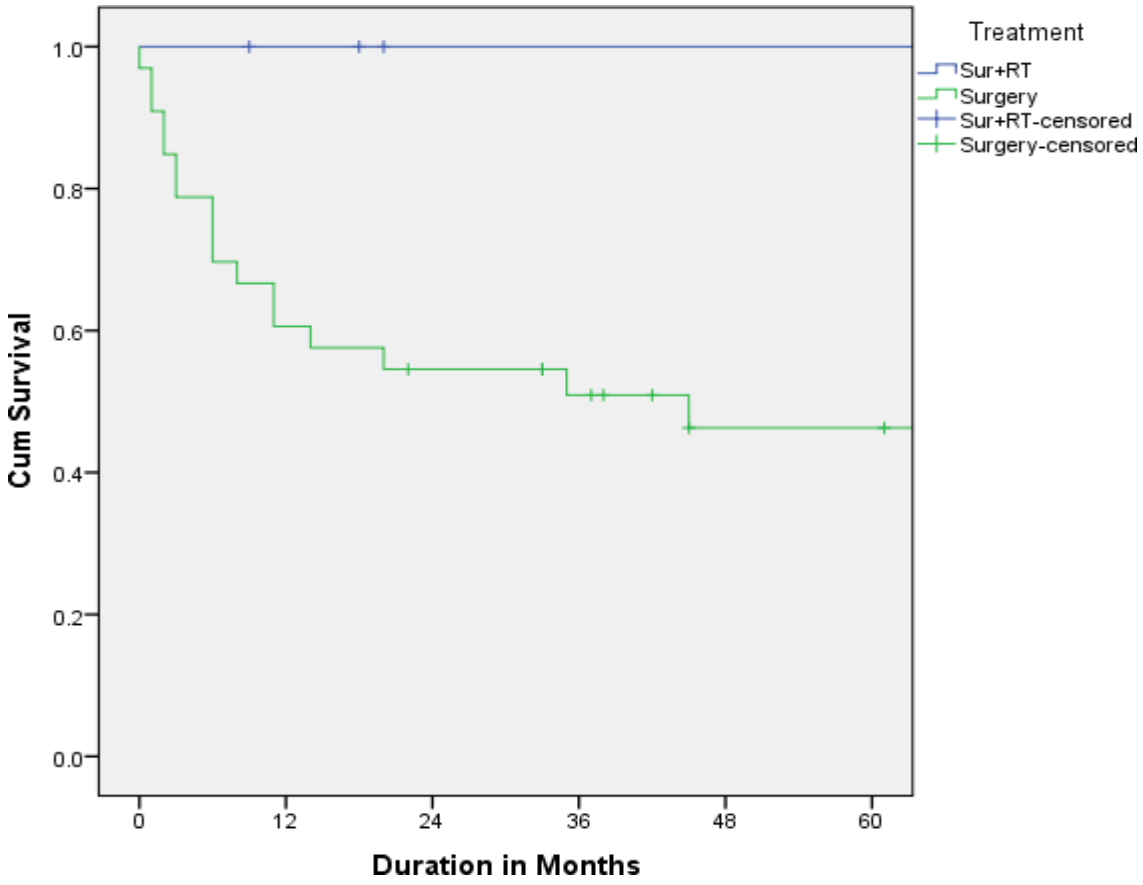


P Value: 0.001

Table 15: Case processing summary for DFS analysis of intermediate risk group

Treatment	Total N	N of Events	Censored	
			N	Percent
Sur+RT	11	0	11	100.0%
Surgery	33	17	16	48.5%
Overall	44	17	27	61.4%

Figure 19: Kaplan-Meier Disease-Free Survival curve for intermediate risk group

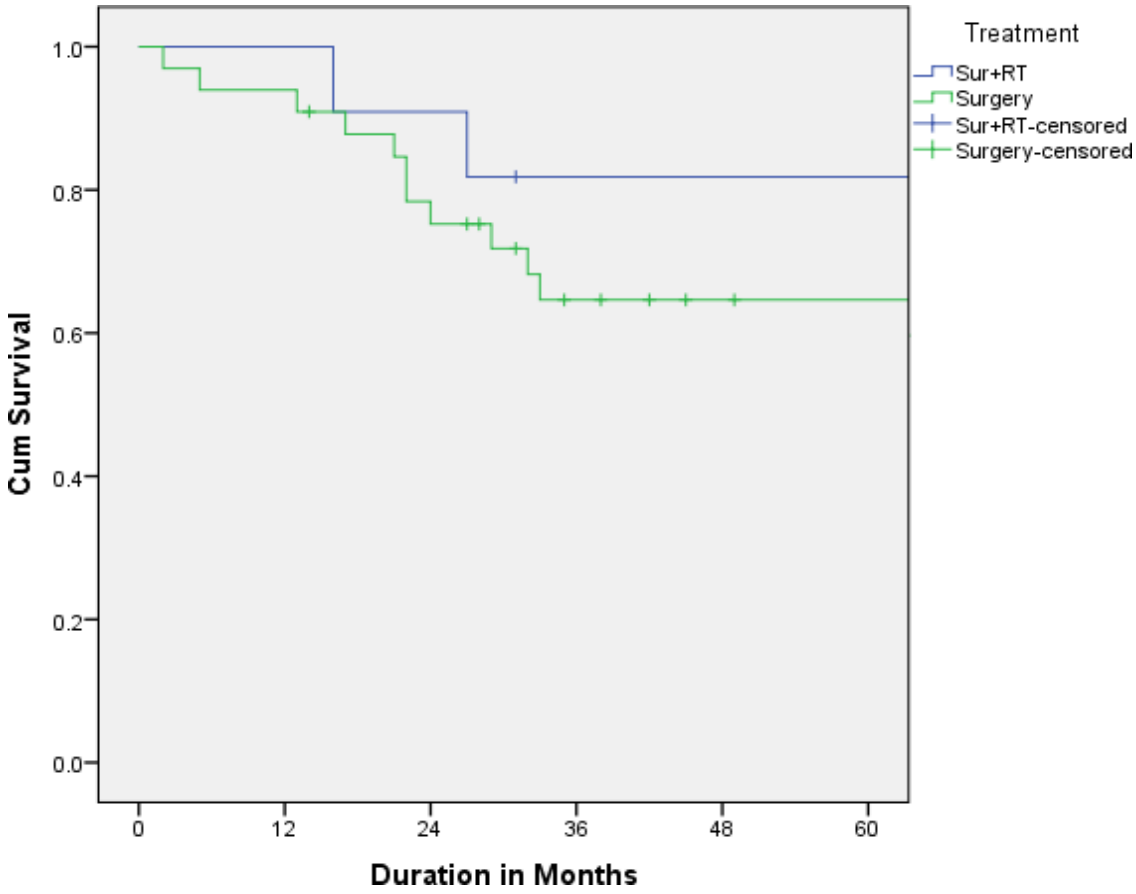


P Value : 0.006

Table 16: Case processing summary for OS analysis of intermediate risk group

Treatment	Total N	N of Events	Censored	
			N	Percent
Sur+RT	11	2	9	81.8%
Surgery	33	13	20	60.6%
Overall	44	15	29	65.9%

Figure 20: Kaplan-Meier Overall Survival curve for intermediate risk group

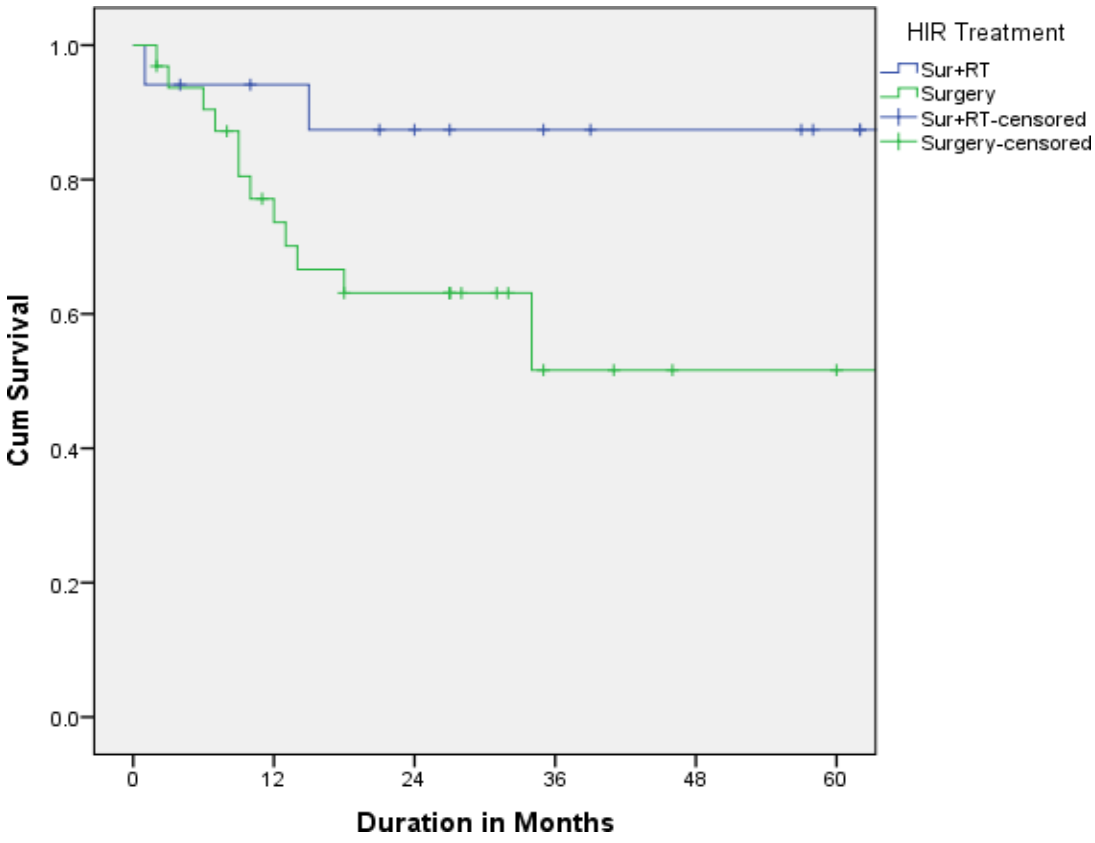


P Value : 0.174

Table 17: Case processing summary for DFS analysis of high -intermediate risk group

Treatment	Total N	N of Events	Censored	
			N	Percent
Sur+RT	15	0	15	100.0%
Surgery	34	15	19	55.9%
Overall	49	15	34	69.4%

Figure 21: Kaplan-Meier Disease-Free Survival curve for high – intermediate risk group

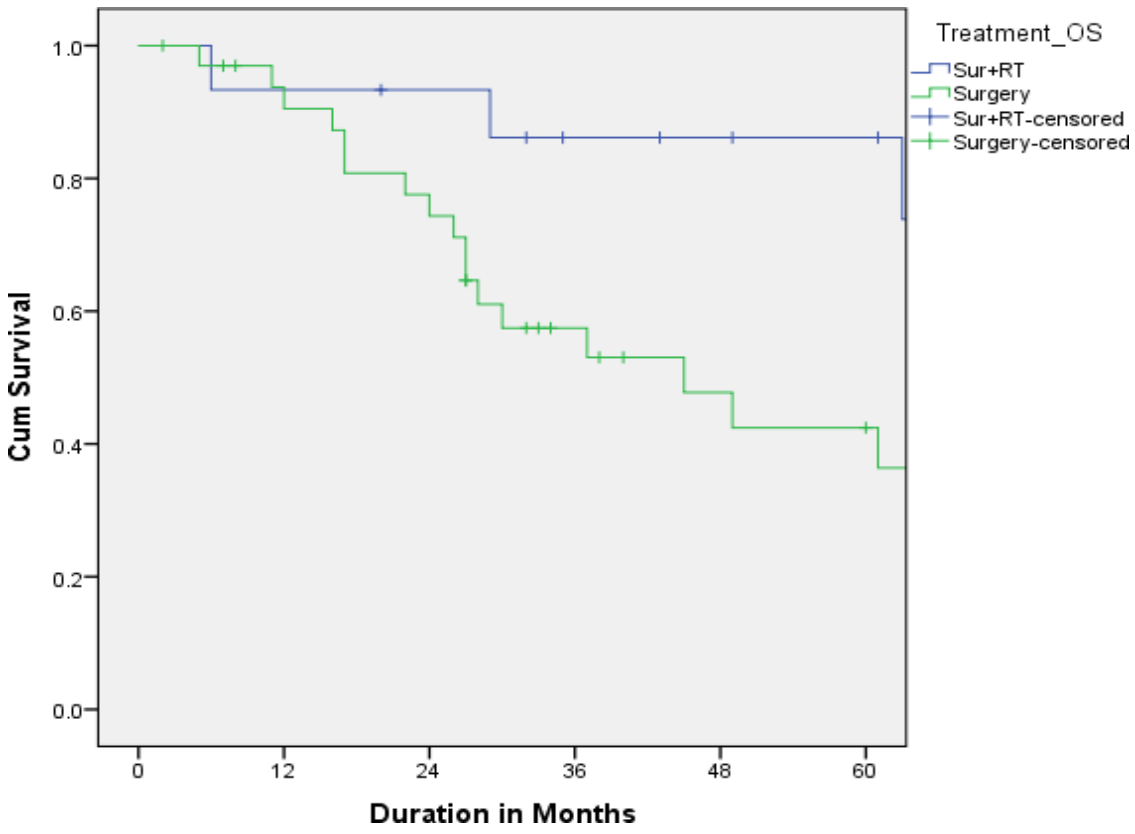


P Value : 0.041

Table 18: Case processing summary for OS analysis of high -intermediate risk group

Treatment	Total N	N of Events	Censored	
			N	Percent
Sur+RT	15	5	10	66.7%
Surgery	34	17	17	50.0%
Overall	49	22	27	55.1%

Figure 22: Kaplan-Meier Overall Survival curve for high – intermediate risk group

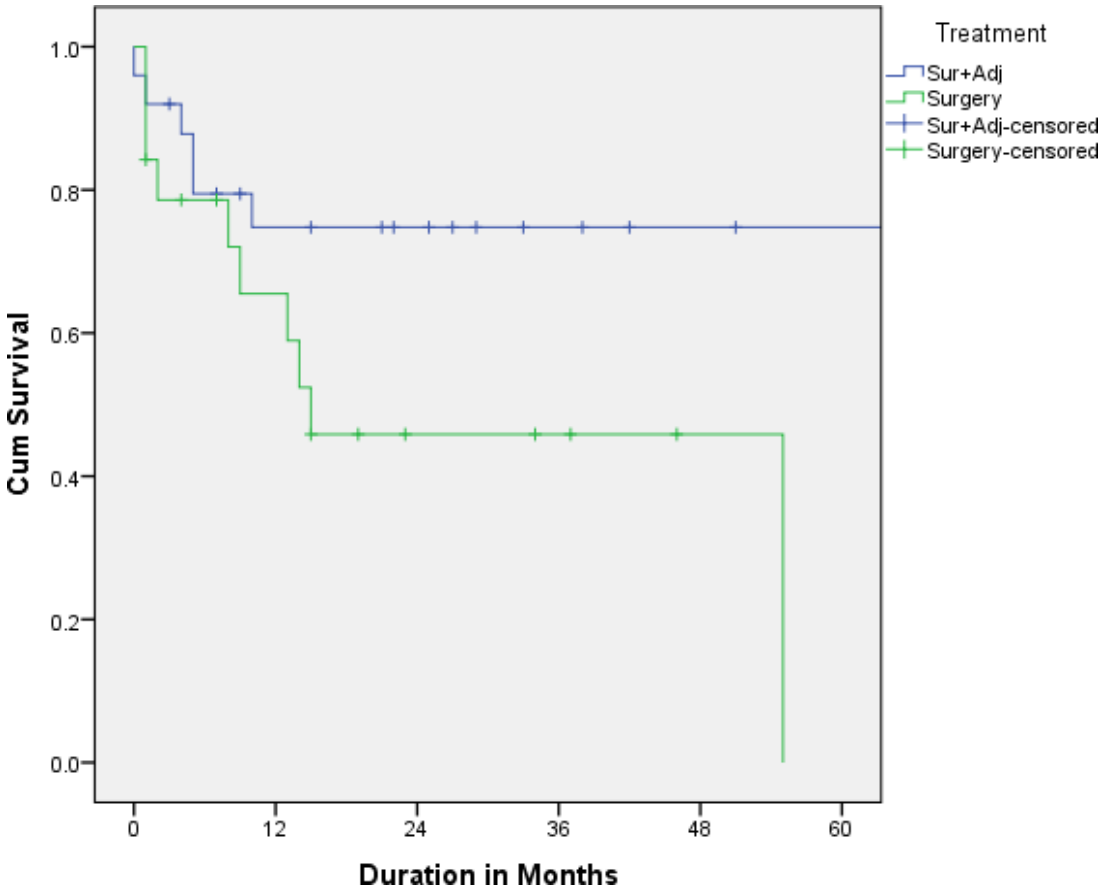


P Value : 0.087

Table 19: Case processing summary for DFS analysis of high risk group

Treatment	Total N	N of Events	Censored	
			N	Percent
Sur + Adj	22	3	19	86.4%
Surgery	22	13	9	40.9%
Overall	44	16	28	63.6%

Figure 23: Kaplan-Meier Disease-Free Survival curve for high risk group

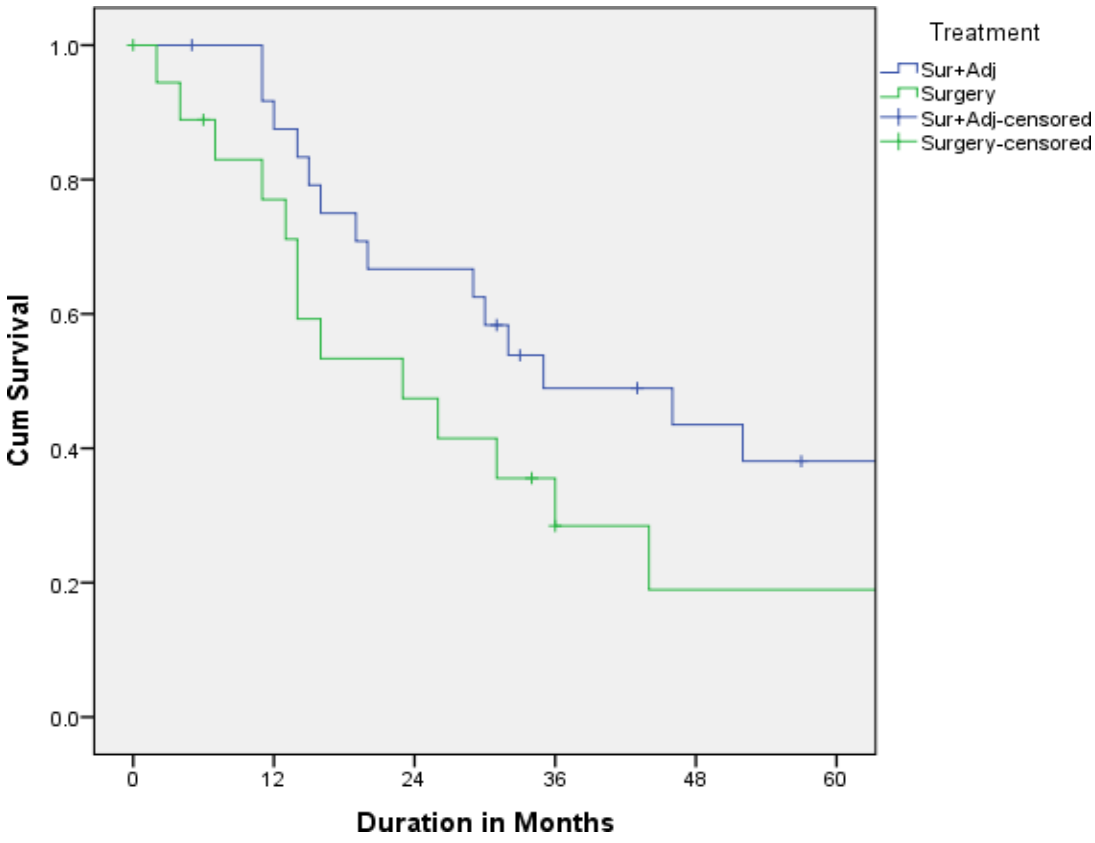


P Value : 0.041

Table 20: Case Processing Summary for OS analysis of high risk group

Treatment	Total N	N of Events	Censored	
			N	Percent
Sur+ Adj	22	14	8	36.4%
Surgery	22	15	7	31.8%
Overall	44	29	15	34.1%

Figure 24: Kaplan-Meier Overall Survival curve for high risk group.

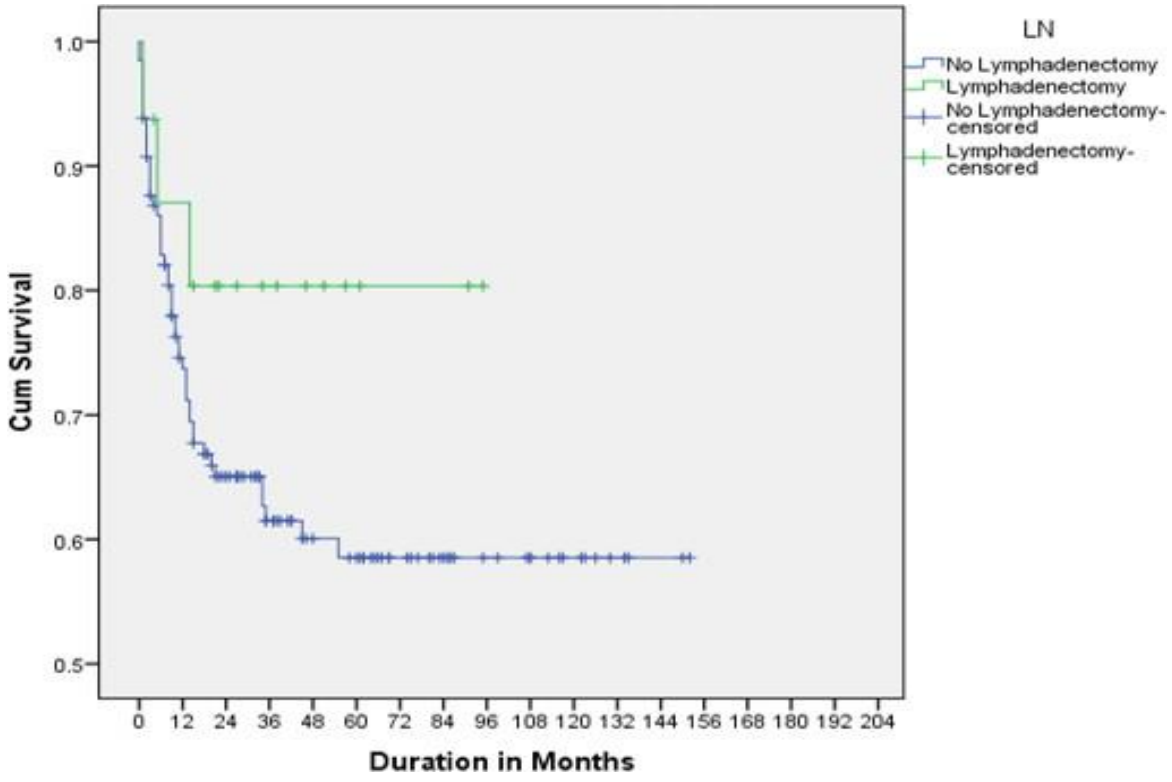


P Value : 0.138

Table 21: Case Processing Summary for DFS analysis of lymphadenectomy vs no lymphadenectomy

LN	Total N	N of Events	Censored	
			N	Percent
NO	130	48	82	63.1%
YES	16	3	13	81.2%
Overall	146	51	95	65.1%

Figure 25: Kaplan-Meier Disease Free Survival for lymphadenectomy vs no lymphadenectomy

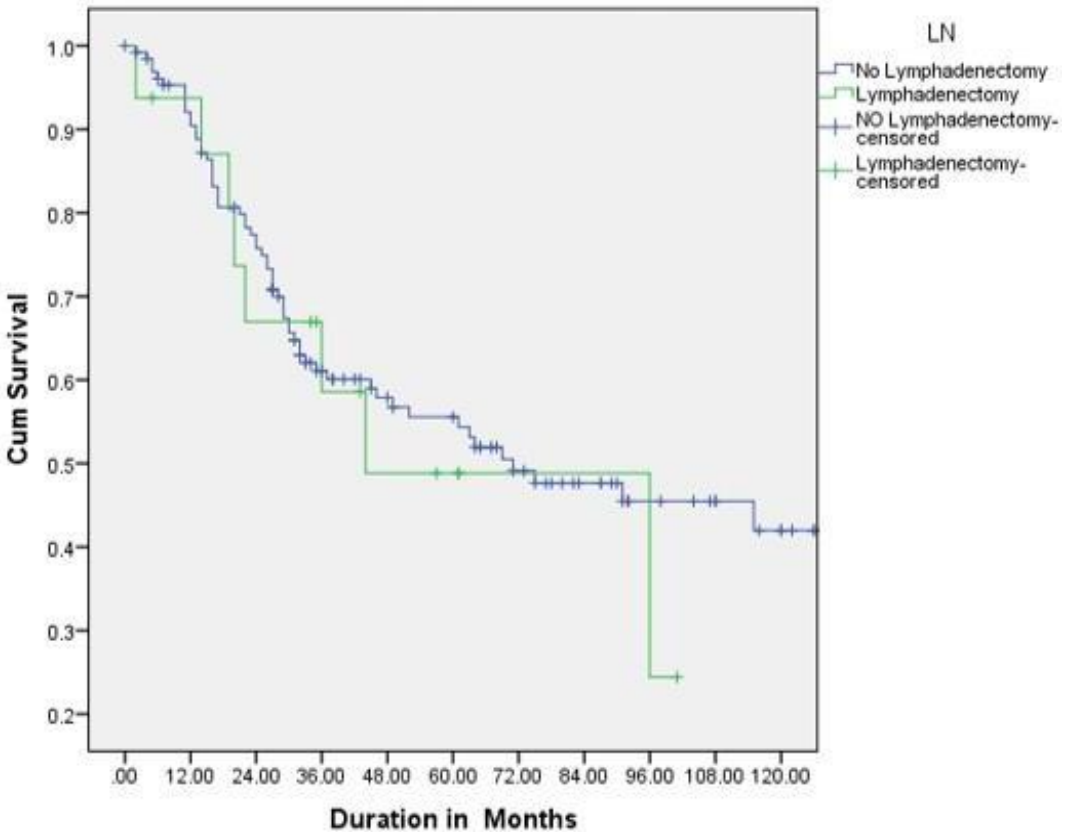


P value : 0.186

Table 22: Case Processing Summary for OS analysis of lymphadenectomy vs no lymphadenectomy

LN	Total N	N of Events	Censored	
			N	Percent
NO	130	60	70	53.8%
YES	16	8	8	50.0%
Overall	146	68	78	53.4%

Figure 26: Kaplan-Meier Overall Survival for lymphadenectomy vs no lymphadenectomy



P value : 0.627

4.6 Recurrence

Recurrenec rate was calculated as the proportion of individuals with re- appearance of disease of the same histology either at the vault, within the pelvis or outside the pelvis as at 31st December 2020.

Recurrences were analyzed according to first site of recurrence as well as the total number of recurrences and stratified into vault (limited to vaginal vault only), pelvic (pelvic with or without vault recurrence) and distance (outside the region of the pelvis).

After a median follow up of 34.5 months, there were 51 recurrences in the whole group giving a recurrenec rate of 35% (Figure 27) . The commonest site of recurrence was the pelvis(25, 49%) (Figure 28). With respect to risk groups, recurrence rates were 33.3%, 38.6%. 30.6% and 36.4% in low, intermediate, high- intermediate and high risk respectively (Figure 29). This recurrence rates in the various risk groups was not found to be significantly different (Table 23).

Vault recurrenec rate was noted to decrease with increasing risk group ie 22%, 14%, 8% and 2% whiles distant recurrence rate increased with increasing risk groups ie (0%, 7%, 10%, 11%). Pelvic recurrence was most common in all risk groups except low risk (Figure 30). For patients who received no adjuvant therapy, recurrenec ratyes were 44%, 41% and 47% in intermediate, high intermediate and high risk groups compared to 17%, 12% and 28% in tose who had adjuvant therapy.clearly showing the effect of adjuvantbtherapy on recurrenec for all risk groups except for low risk (Figure31).

The site of recurrence has a stitistically significant impact on survival. The 2 year overall survival for patients with vault, pelvic and distance recurrence were as follows 90%, 48% and 42% whiles that at 5 years was 64%, 14 % and 10% (P – value: 0.007) (Figure 32).

Figure 27: Recurrence rate in all patients

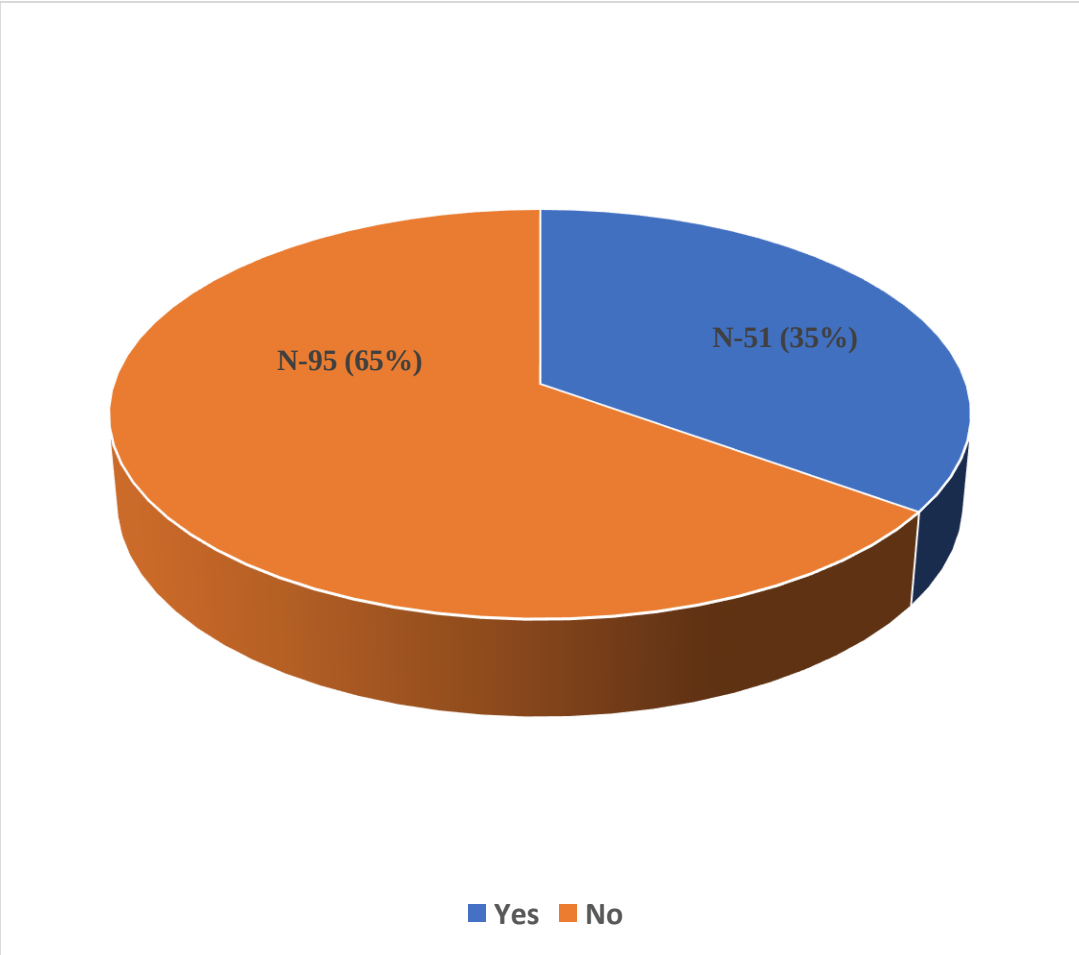


Figure 28: Site of recurrence

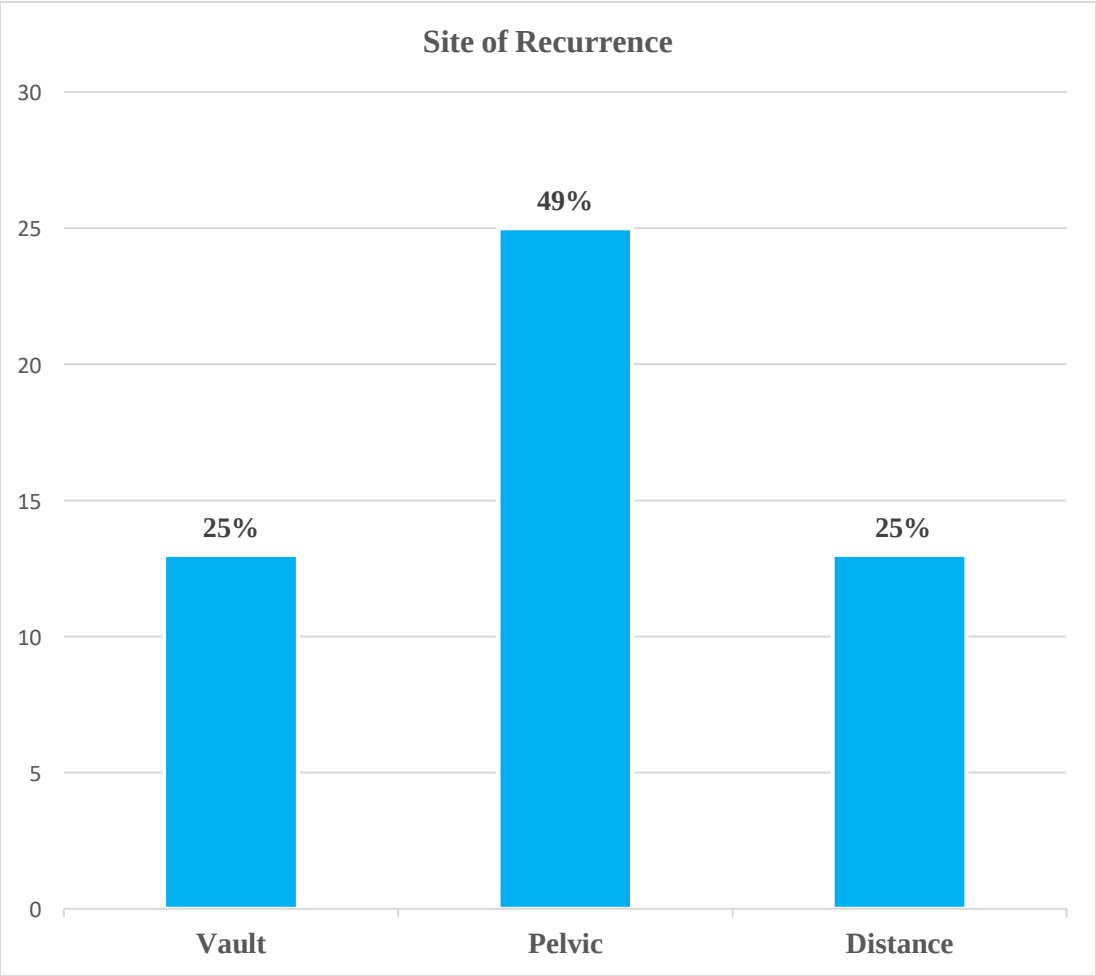


Figure 29: Recurrence rate according to risk groups

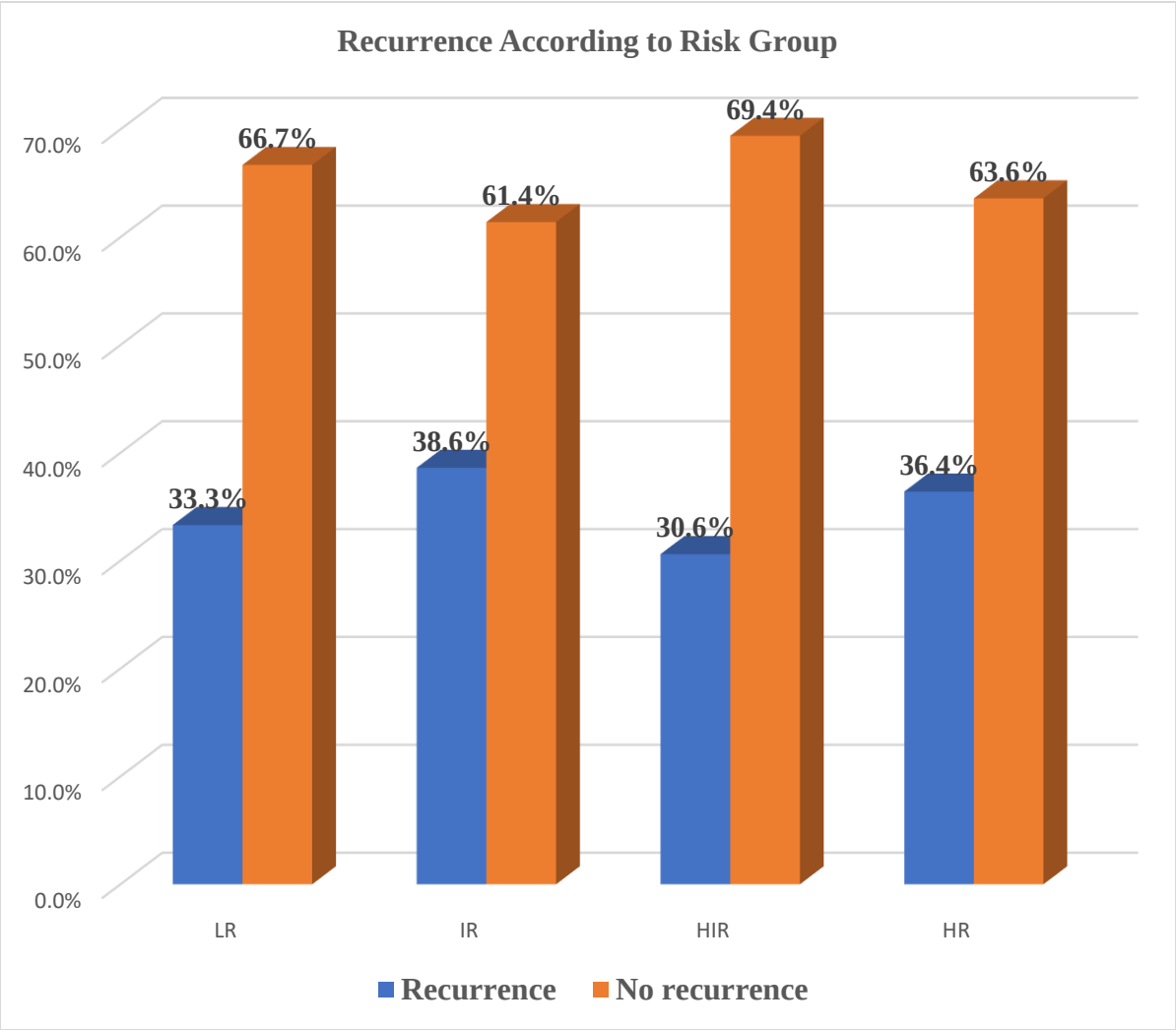


Table 23: Association between recurrence and Risk groups (chi-squire analysis)

Recurrence	Low Risk	Intermediate	High Intermediate	High Risk	Total	P-value
Yes	3	17	15	16	51	
No	6	27	34	28	95	**0.884**
Total	**9**	**44**	**49**	**44**	**146**	

Figure 30: Patterns of recurrence according to risk groups

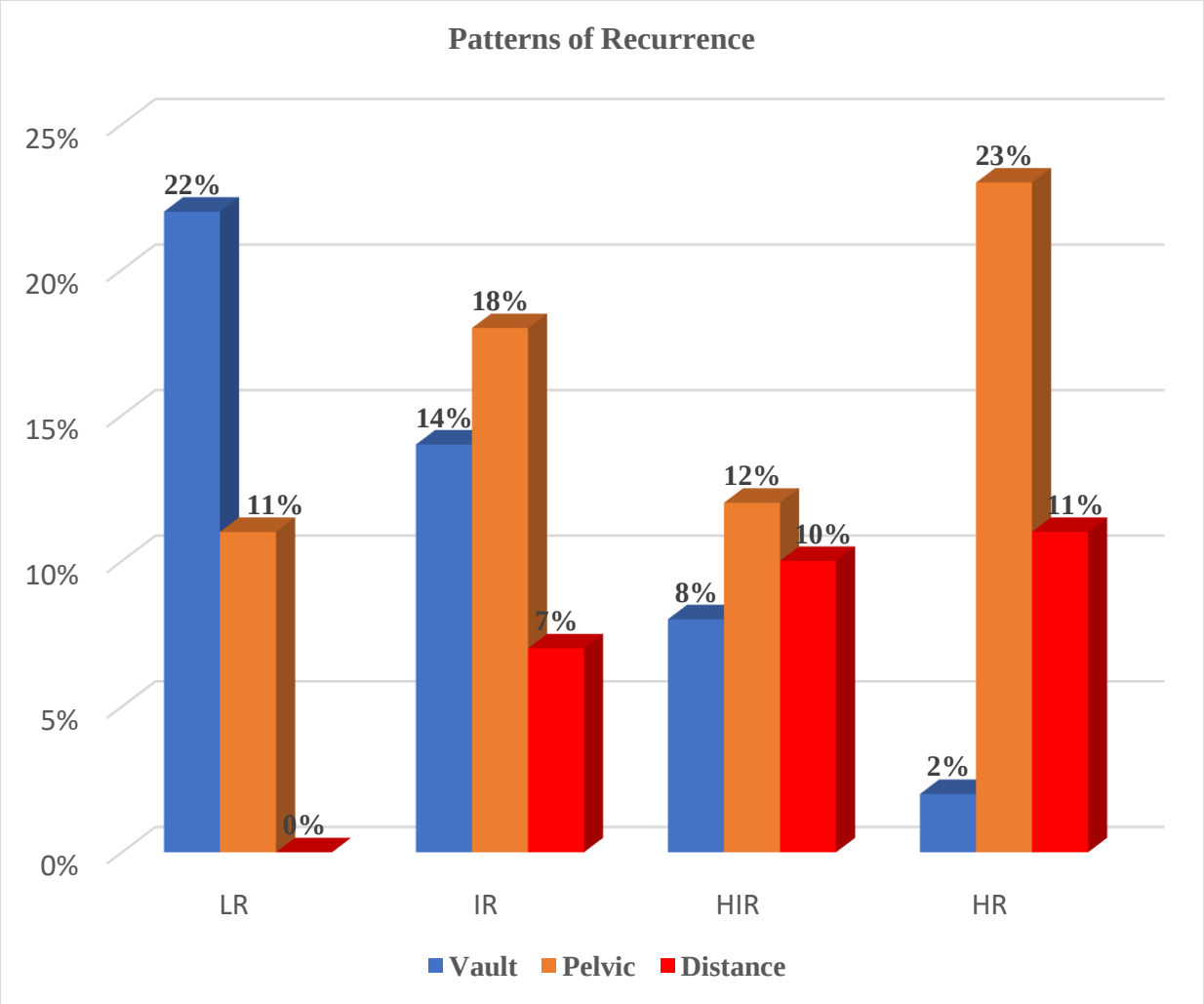


Figure 31: Recurrence rates (Surgery only vs adjuvant therapy)

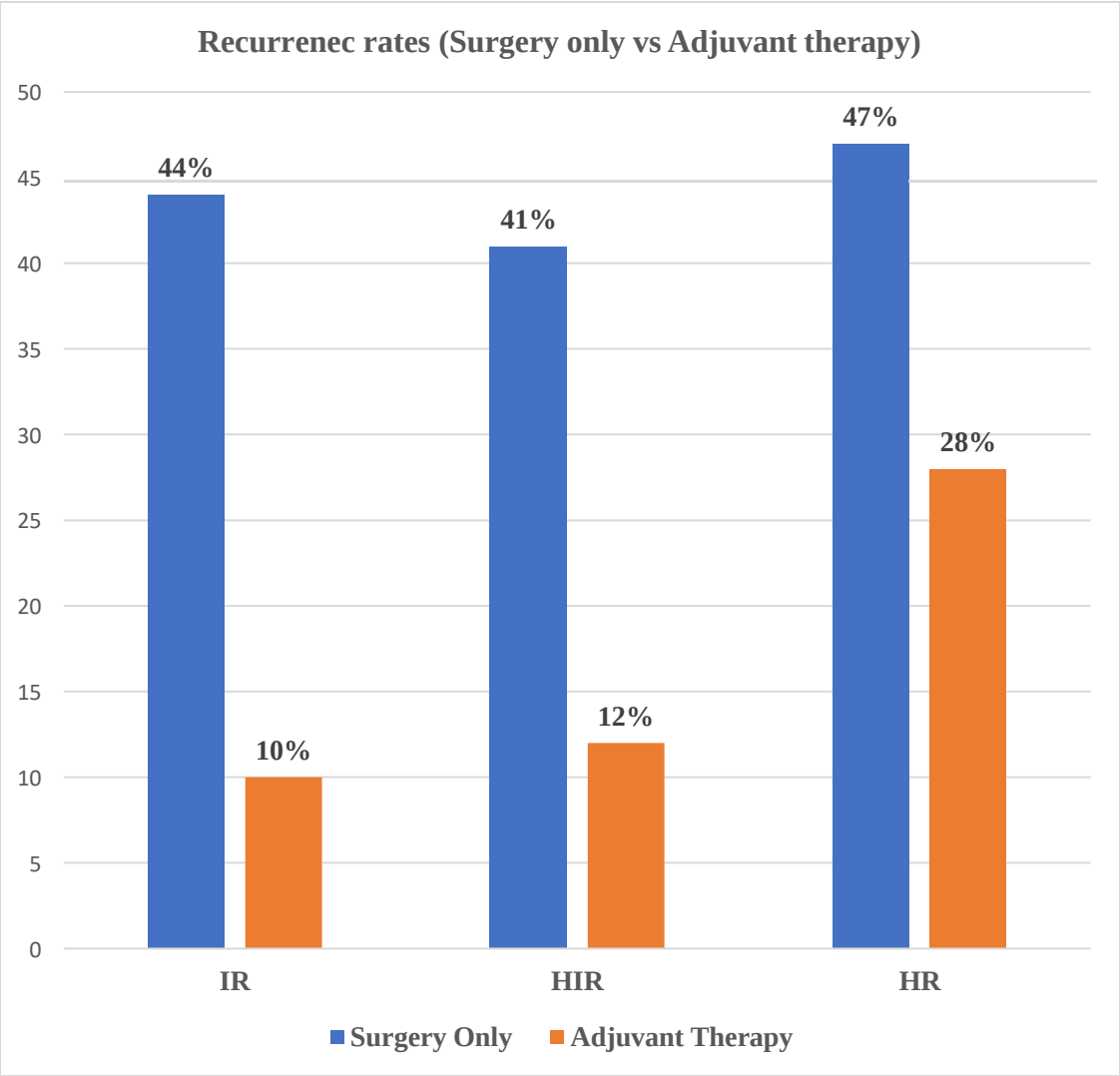
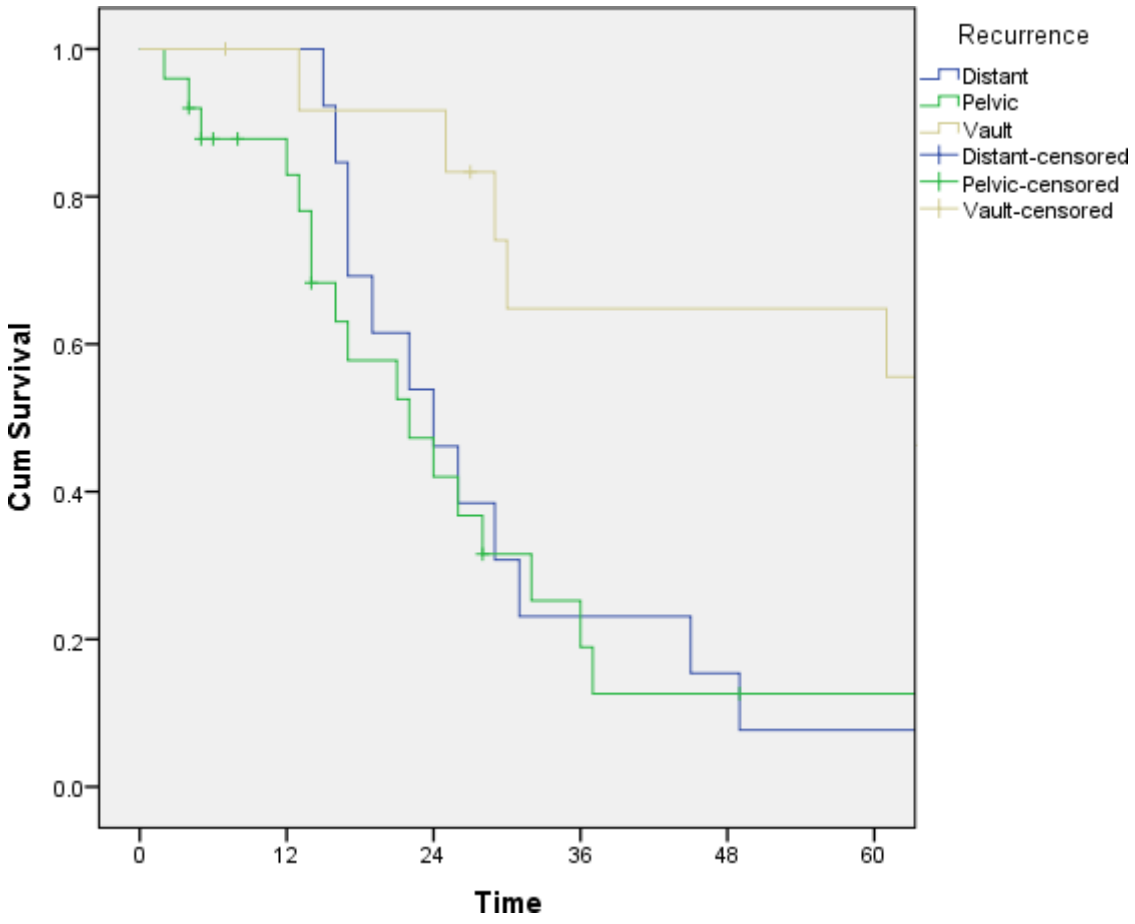


Figure 32: Overall Survival for different sites of recurrence



P Value : 0.007

4.7: Socio-demographic factors associated with survival (Disease-free and overall survival)

Tables 24 show that, from a Cox regression analysis of the data, there was no statistically significant association between the socio-demographic factors: marital status, religion or educational level and disease-free survival.

Marital status was the only factor that had a significant association with overall survival (p-value:0.037). The other factors; religion and educational level had no association with overall survival (Table 25).

Table 24: Socio-demographic factors associated with disease-free survival

	Sig.	HR	95.0% CI	
			Lower	Upper
Marital Status	.277			
Single/Married	.702	.840	.345	2.048
Divorced/Married	.722	1.210	.424	3.454
Widow/Married	.120	.325	.079	1.341
Education	.238			
None/Basic	.210	.580	.248	1.358
Secondary/Basic	.138	.501	.201	1.250
Tertiary/Basic	.952	1.021	.514	2.029
Religion	.511	.724	.276	1.897

Table 25: Socio-demographic factors associated with overall survival

	Sig.	HR	95.0% CI	
			Lower	Upper
Marital Status	.037			
Single/Married	.043	3.373	1.038	10.958
Divorced/Married	.018	4.724	1.308	17.065
Widow/Married	.564	1.528	.362	6.449
Education	.228			
None/Basic	.174	.586	.271	1.267
Secondar/Basic	.464	1.301	.643	2.632
Tertiary/Basic	.904	.961	.502	1.839
Religion	.208	1.831	.714	4.697

4.8: Clinicopathological factors associated with recurrence

A univariate analysis for loco-regional and distant recurrence was run for all clinico-pathological variables, which included age, stage, grade, lymphovascular invasion and histological type of endometrial cancer (Table 26-30).

Of these variables, the only one that had an association with recurrence was lymphovascular invasion (p-value:0.011).

Table 26: Association between Age groups and recurrence

Age Group	Recurrence			Total	P-Value
	Vault	Pelvic	Distant		
<50	4	4	1	9	0.277
50 – 59	13	13	6	25	
60 – 69	5	5	6	14	
≥70	3	3	0	3	
Total	13	25	13	51	

Table 27: Association between FIGO stage and recurrence

Stage	Recurrence			Total	P-Value
	Vault	Pelvic	Distant		
1a	3	2	0	5	**0.511**
1b	7	8	5	20	
2	2	5	4	11	
3a	1	7	3	11	
3b	0	1	0	1	
3c	0	2	1	3	
Total	13	25	13	51	

Table 28: Association between grade and recurrence

Grade	Recurrence			Total	P-Value
	Vault	Pelvic	Distant		
1	4	4	1	9	**0.277**
2	13	13	6	25	
3	5	5	6	14	
Not Stated	3	3	0	3	
Total	13	25	13	51	

Table 29: Association between LVI and recurrence

LVI	Recurrence			Total	P-Value
	Vault	Pelvic	Distant		
Yes	11	22	6	39	**0.011**
No	2	3	7	12	
Total	13	25	13	51	

Table 30: Association between histological type and recurrence

Histology	Recurrence			Total	P-Value
	Vault	Pelvic	Distant		
Clear Cell Carcinoma	0	0	1	1	0.336
Endometrial Stromal Sarcoma	0	0	1	1	
Endometrioid Adenocarcinoma	5	15	6	26	
Leiomyosarcoma	2	5	3	10	
Papillary Adenocarcinoma	5	3	1	9	
Serous Papillary Carcinoma	1	2	1	4	
Total	13	25	13	51	

4.10: Clinicopathological factors associated with survival (Disease-free and overall survival)

To assess the clinico-pathological factors associated with disease-free and overall survival, a Cox regression analysis was run (Tables 31 and 32).

Histopathological type was the only factor associated with disease-free survival. No association was found between Age, FIGO Stage, grade and lymphovascular invasion.

With respect to overall survival, FIGO stage, grade and Histology subtype were found to be associated, whiles LVI and age was not.

Table 31: Clinicopathological factors associated with disease-free survival

	Sig.	HR	95.0% CI	
			Lower	Upper
Grade	.072			
½	.696	1.320	.328	5.314
1/3	.125	2.681	.760	9.450
grade 1 / Not Stated	.065	3.378	.929	12.285
Stage	.197			
1a / 1b	.892	1599.928	.000	2.807E+049
1a / 2	.893	1530.389	.000	2.682E+049
1 a / 3a	.896	1191.895	.000	2.090E+049
1a / 3b	.876	4765.076	.000	8.350E+049
1a / 3c	.874	5663.403	.000	1.011E+050
1a / 4a	.888	2117.963	.000	3.727E+049
LVI	.224	.631	.301	1.325
Histology	.007			

Endometrioid adenocarcinoma/ Clear Cell Carcinoma	.919	1100.212	.000	5.304E+061
Endometrioid adenocarcinoma / Neuroendocrine carcinoma	.885	21747.691	.000	1.034E+063
Endometrioid adenocarcinoma / Papillary adenocarcinoma	.950	1338.743	.000	1.675E+100
Endometrioid adenocarcinoma / Serous Papillary Carcinoma	.898	6910.817	.000	3.287E+062
Endometrioid adenocarcinoma / Undifferentiated Carcinoma	.911	2289.549	.000	1.091E+062
Age	.219			
<50 / >70	.085	.347	.104	1.155
<50 / 50 – 59	.285	.542	.176	1.669
<50 / 60 -69	.987	1.006	.506	2.001

Table 32: Clinicopathological factors associated with overall survival

	Sig.	HR	95.0% CI	
			Lower	Upper
Grade	.039			
½	.019	.286	.100	.813
1/3	.316	.634	.260	1.545
grade 1 / Not Stated	.824	.902	.362	2.246
Stage	.050			
1a / 1b	.067	.206	.038	1.117
1a / 2	.159	.323	.067	1.555
1a / 3a	.075	.235	.048	1.154

1a / 3b	.605	.649	.126	3.350
1a / 3c	.650	1.659	.186	14.771
1a / 4a	.537	.578	.102	3.295
LVI	.811	.922	.472	1.799
Histology	.029			
Endometrioid adenocarcinoma/ Clear Cell Carcinoma	.934	1.113	.088	14.146
Endometrioid adenocarcinoma / Neuroendocrine carcinoma	.331	3.415	.287	40.656
Endometrioid adenocarcinoma / Papillary adenocarcinoma	.377	.212	.007	6.626
Endometrioid adenocarcinoma / Serous Papillary Carcinoma	.568	.488	.041	5.740
Endometrioid adenocarcinoma / Undifferentiated Carcinoma	.527	.463	.042	5.043

Age	.059			
<50 / >70	.007	.195	.059	.643
<50 / 50 – 59	.887	.942	.417	2.132
<50 / 60 -69	.215	.648	.327	1.285

CHAPTER FIVE

5.0 Discussion

Endometrial cancer has been ranked as the third commonest genital tract cancer after cervical and ovarian malignancies in Ghana.[4] However, at the National Radiotherapy, Oncology and Nuclear medicine Centre, EC accounted for 16.8% of all gynaecologiocal cancers between 2009 and 2018, making it the second most common female genital tract cancer according to the hospital-based registry. A total of two hundred and sixty-nine patients were seen, however 146 were eligible for analysis. Most of the sample population were literate economically active women, who were married and belonged to the Christian religion.

The average age of the sample population was 61.3 years (Std dev 9.0) with incidence peak age group being 60 to 69 years and 10% less than 50 years**.** Endometrial cancer risk has been found to have a positive correlation with age[25] with more than 90% of cases diagnosed after the age of 50 years[92] which correlated with our study results. Incidence peaks however differs by targeted study population, country, race as different studies have shown different incidence peaks [93 - 95].

The study attempted to assess some possible risk factors in this population including age at menarche and menopause, post - menopausal Body Mass Index (BMI) and the prevalence of hypertension and diabetes.

The mean age at menarche was 15.2 years (std dev 1.8) while that of menopause was 50 years (std dev.3.5). The lifetime number of years of menstruation for postmenopausal women in this study population was 35.2 year (srd dev 4.1). 8.6% were nulliparous whiles both mean and median number of live births was 3 (Range 1-11). The mean age at menarche among Ghanaian women has been reported in different studies to be 13.89+-1.42 years[96,], 12.74 ± 1.15[97] whiles that of menopause has been reported to be 48.05 years +/- 3.62[98] Literature search did not reveal any study on lifetime years of menstrual cycles in Ghana. Menarche occurring early in life, while menopause later in life, increases the number of menstrual cycles and, as a result, the overall amount of oestrogen exposure time.[29] When compared to women who reach menarche at or after the age of fifteen, those who reach menarche earlier have a nine-fold increased chance of having endometrial cancer.[29] Women who went through menopause between the ages of 50 and 54 had a 67% higher risk of endometrial cancer than women who went through menopause before the age

of 45, according to Setiawan and colleagues[30]. Several studies have reported a positive correlation between lifetime years of menstrual cycle and incidence of EC[99-101]. The observation made from this study was that of a fairly late age at menarche and also a late age at menopause. This late age at menopause may not have led to a higher risk in these women due to their late age at menarche and the contribution of high parity leading to a reduction of overall number of menstrual cycles resulting in less estrogen exposure.

Average BMI was 28.2mg/m^2 (std dev 6.1). Majority of patients, (117, 67%) were above normal BMI with 35% being obese. It may be even possible that these women had higher pre-diagnosis BMI than what was observed due to the weight loss that is sometimes experienced after major surgeries like TAH and BSO with or without lymphadenectomy, as well as change in dietary lifestyles practiced by many patients after diagnosis of cancer. Obesity has been linked to an increased risk of endometrial cancer in both pre-menopausal and post-menopausal women.[31] The conversion of testosterone to oestrogen in excess adipose tissue raises circulating endogenous oestrogens.[32] In comparison to women with a normal BMI, obese women have a 2–22 fold increased chance of having endometrial cancer.[35] It is however important to note that the BMI distribution observed in this study was quite similar to the results of the Women's Health Study published in 2012 which reported that 64.9% of 2,814 women sampled were either overweight or obese[102] implying that BMI alone may not be a risk factor in this study population compared to other Ghanaian women.

Prevalence of hypertension and diabetes within the group was 57% and 20% respectively. Hypertension was the leading cause of deaths in Ghana in 2017 accounting for 15.3% of total deaths[103]. A recent meta-analysis put the pooled prevalence of hypertension to be 27% (95% CI 24.0%-30.0%) [104]. Studies have given estimates of between 3.3 and 6% of the general Ghanaian population having diabetes with the prevalence increasing with age and being lower in rural areas than urban[105 -107]. It can be argued that, the obviously higher prevalence of hypertension and diabetes in the study population might be a strong risk factor for endometrial cancer in these women.

In summary, late age at menopause, high BMI, hypertension and diabetes were some of the common risk factors that we observed in our study population. It was however impossible to

determine the exact effect of these factors on the development of endometrial cancer because of the study design employed. Case control studies may have to be conducted in order to determine the correlation between these factors and endometrial cancer in Ghanaian population.

Abnormal vaginal bleeding was the commonest presenting symptom accounting for 78.9% of all presenting complaints. This comprised of post - menopausal bleeding (72.7%), menorrhagia (5.1%) and intermenstrual bleeding (1.1%). Following this was vaginal discharge and abdominal pain (6.8%). Most women (54%) reported to the health facility less than six months after the initial symptom. A significant number (28, 15.9%) however delayed for over 12 months. The most common presentation for endometrial cancer is postmenopausal bleeding although incidence of EC in women presenting with post- menopausal bleeding is only 10-15%. In a report of a total of 3,548 women who presented with postmenopausal bleeding, recurrent episodes of bleeding increased the risk (OR-3.64) of EC when multiple logistic regression model was used[108]. Many of the women (46%) in the study reported after 6 months of recurrent bleeding. Late presentation is one of the major problems associated with cancer management in developing countries leading to advanced stage and poor outcome. Late stage at presentation goes beyond educational level as can be seen in this study and is compounded by cultural practices and widespread use of alternative medicines[109]. It is therefore not surprising that less than half (47%) of the patients had FIGO stage I disease, 30% with stage II, 21% stage III and 2% stage IV. In contrast, a study conducted in Nigeria reported stage I disease to comprise 62% of the total number of cases[110].

Endometrioid adenocarcinoma was the major histological type (79.5%). This result is in agreement with the classical presentation of adenocarcinoma in other settings. For example, in the US, adenocarcinoma comprised over 90% of all cases[111].

All patients had total abdominal hysterectomy and bilateral salpingo–oophrectomy with or without lymph node dissection. Pelvic and para- artic lymph node dissection is not routinely practiced in Ghana. The choice of whether or not to do lymph node dissection is entirely dependent on the attending gynaecologist's preference as well as skill. Many surgeons have not embraced full lymphadenectomy because of the lack skill and justified by lack of survival benefit.

The lymph node dissection rate among the sample population was 11% with an average of 19 pelvic lymph nodes (SD 13.7) and 6 (SD 2.6) para –artic lymph nodes sampled. The wide standard deviation reflects the wide range of skill in the area of lymph node dissection by attending gynaecologist. Of note however, is the observation that the proportion of patients with positive lymph nodes was 62.5%. This far exceeds the lymph node positivity rate of 2.4%, 9% and 24% in low, intermediate and high risk early stage EC groups reported in the MRC- ASTEC study [62]. Survival analysis was run to compare outcome of patients who had lymphadenectomy with those who did not. Although 5 year DFS was better in patients who had lymphadenectomy (81% vs 58%) , it was not significant (p-value: 0.18). Overall survival was not significantly different between the two groups either. The high lymph node positivity rate brings up the question of whether lympadenectomy should be considered in all patients with endometrial carcinoma in our setting. Prospective randomized control trials are needed in Ghana to further investigate the effect of lymphadenectomy on recurrence and survival according to risk groups.

Many demographic and histological characteristics have been linked to an increased risk of recurrence, including increasing age, depth of myometrial invasion, histological tumor type and grade, presence of LVSI, and FIGO classification. These criteria have been compiled into several risk stratification systems (RSS) that are now used to guide decision-making around the world. The assumption is based on the creation of recurrence risk groups, which can aid in identifying clinical situations in which adjuvant therapy for high-risk patients or, conversely, surveillance following surgery for low-risk patients. Patients were risk stratified using the PORTEC method in this study. Adjuvant therapy was chosen based on risk assessment and the attending physician's preference. External beam radiation (EBRT) to the pelvis +/- vaginal brachytherapy +/- chemotherapy were used as adjuvant treatments.

Patients who fell within the low-risk category were offered no adjuvant therapy after surgery. Within the low intermediate risk group, the addition of adjuvant therapy was entirely based on the discretion of attending oncologist. Whiles the majority of patients received no adjuvant therapy, approximately 27% had adjuvant external beam radiotherapy +/- vaginal brachytherapy. In the high intermediate risk group, only one third of the patients received adjuvant radiotherapy whiles the remaining two thirds defaulted. The same was seen in the high risk

population, where approximately half of the patient defaulted adjuvant therapy which involved EBRT to pelvis +/- vaginal brachytherapy and chemotherapy. The cost of cancer treatment is not fully covered by national or private health insurance plans, necessitating hefty out-of-pocket payments as well as the stress of daily treatment travel. These are only a few of the significant factors that have contributed to the high default rate. The inclusion of cancer treatment in the national health insurance policy, as well as comprehensive patient education and the implementation of patient support services, may all aid in lowering the high default rate seen among these patients.

Based on the PORTEC criteria, we identified 9 low, 44 LIR patients, 49 HIR patients, and 44 high-risk patients. There was no significant difference in DFS ($p<0.74$) among the four groups. This was an interesting finding and brings to question the validity of the PORTEC as well as the other risk stratification systems (RSS) in assessing the risk of recurrence in EC in our population. Practice patterns differ widely among oncologists in the management of patients with EC. This is mainly due to the several criteria defining risk groups for recurrence. Several authors have devised RSS to build a standard nomenclature to circumvent these restrictions and aid doctors in their decision-making[18,112-115]. Although all of these RSS have comparable factors, the combination of variables varies significantly, resulting in very disparate adjuvant therapy practice patterns. A classification's predictive accuracy is based on the premise that all patients in a given risk group are the same. However, variation in biological markers and patient factors have been found within each risk grouping, particularly among women with early-stage EC. Endometrial cancer classification based on molecular profiling may allow us to better stratify risk, evaluate prognosis, and predict treatment response than histology and stage alone. Different molecular classification schema have been devised by Talhouk et al, The Cancer Genome Atlas Collaborative (TCGA), and the GOG 210 investigators[43,44,116] to better stratify patient risk. These molecular tests would have to be included into the present RSS in order to better identify patients at risk of recurrence for direct adjuvant therapy in the future. We noticed a high rate of recurrence in low risk groups which ultimately could be high risk if molecular features had been tested.

Both 2 and 5year disease-free survival in low-risk patients was 67% whiles that for overall survival was 100% and 87.5% respectively. Low-risk disease, generally defined as low-grade

disease limited to the endometrium or with limited MMI, is typically managed with surgery alone with good outcomes. These patients have very good rates of local control with no additional therapy.

Several trials have reported on significant locoregional control in the use of adjuvant radiotherapy in HIR endometrial cancer but not significantly in low Intermediate risk [18,67,68,112]. In this study, 27% of intermediate risk patients received adjuvant radiotherapy (EBRT +/- Brachytherapy) resulting in significantly higher (p-value-0.006) 5year DFS of 100% compared to those who received no adjuvant treatment, 46%. Almost half, 44% of patients who had no adjuvant therapy had recurrent disease within the first two years of surgery, majority of which were pelvic (43%). Many postulations and explanations could be drawn from this finding; the major of which is the validity of the current risk stratification systems in predicting recurrence and hence adjuvant therapy. This finding throws doubts on the current RSS bringing to light the importance of a more advanced molecular classification in our setting. Another theory is the possibility that some cases categorized as intermediate risk, were actually high risk. As stated earlier, the lymph node positivity rate among patients who had lymphadenectomy was as high as 62.5%. Combining this with the fact that most of the recurrences were pelvic, there is the possibility that a large proportion of these intermediate risk population would have fallen into high risk category had lymphadenectomy been done. There are several imaging modalities to help define the extent of disease preoperatively. Abdominopelvic CT Scan obtained with oral contrast can help in determining the extent of endometrial tumour. It is also helpful to assess regional and distant metastasis. Magnetic resonance imaging (MRI) is considered the most accurate imaging study to assess tumour extent, especially myometrial invasion, as well as tumour extension into cervical stroma. MRI however has a poor sensitivity for detecting lymph node metastasis and has been reported to be on average, 43.5%.[128] Sensitivity has however been reported to be 95.9%. Positron emission tomography (PET/CT) is also being used in endometrial acner nut has little benefit in assessing primary tumour extent. With regard to regional lymph nodes metastasis, the reported sensitivity and specificity is 72% and 94% respectively.[129] The standard FIGO staging for endometrial cancer is surgical staging and so preoperative imaging studies are not part of the staging.[130] Although lymphadenectomy has not proven to have any benefit on survival, these findings set a stage for randomized control trials to confirm its benefit in the Ghanaian population.

The benefit seen in DFS for patients who had adjuvant radiotherapy was however not translated into overall survival (75% vs 64.5% at 5years, p-value – 0.17).

Forty –nine women were identified as HIR, of which 35% had adjuvant radiotherapy. The 5year DFS was 87% for the adjuvant radiotherapy group and 52%. (p-value, 0.041) for the no radiotherapy group. This finding confirms that of several phase III trials that supports adjuvant radiotherapy in HIR group to improve locoregional control but not overall survival.[18,67,68,112]. Overall survival was not significantly different in the two groups(p-value,0.087).

Likewise, in the HR group, the 57% of patients who received adjuvant therapy (EBRT +/- Brachytherapy+/-chemotherapy) had significantly improved 2year DFS (70.5% vs 45.5%, p-value-0.041)) but not overall survival (67% vs 47.5% p-value 0.138).

Recurrences were analyzed according to first site of recurrence as well as the total number of recurrences and stratified into vault (limited to vaginal vault only), pelvic (pelvic with or without vault recurrence) and distance (outside the region of the pelvis).

There were 51 recurrences in the whole group giving a recurrenec rate of 35%, with the commonest site of recurrence being the pelvis(25, 49%). With respect to risk groups, recurrence rates were 33.3%, 38.6%. 30.6% and 36.4% in low, intermediate, high- intermediate and high risk respectively These recurrence rates in the various risk groups was not found to be significantly different. The rates far exceed that reported in other studies[18,67,68,112] and may likely be due to the large number of HIR and HR patients who did not receive adjuvant radiotherapy. Not only is the high recurrence rate of concern but also the sites of recurrence. Aside low risk group where the vaginal vault was the commonest site, the pelvis was the commonest in all the other risk groups. The very low vault recurrence seen especially in the high risk group is likely the result of very low survival rate in this group and consequently short follow up period to express these recurrence. In the group that had surgery only, less than half were alive at 2 years. Vaginal recurrences are the most common type of recurrence in all risk groups, and they're also the most treatable if caught early. It is possible that many patients harbored microscopic lymph node disease which later progressed to overt recurrences. This is supported by the finding of high lymph node positivity rate in the cohort of patients who had lymphadenectomy.

Distance metastasis accounted for 25% of all recurrences. The lung was the commonest (46%) site followed by the liver (39%) and supraclavicular lymph node (23%). The rate of distance metastasis increased with increasing risk category of EC. When compared to other gynecologic cancers, endometrial carcinoma has the highest rate of pulmonary metastases, up to 20%–25%. Bilateral nodules are common, however a solitary nodule that looks like primary lung cancer can also be detected. Cavitation is also a possibility, notably in squamous cells.[117,118]

Survival of patients with recurrence was dependent on site of recurrence as well as previous treatment received. Patients with vault only disease after surgery were offered pelvic radiotherapy, followed with vaginal brachytherapy e ither with LDR or HDR brachytherapy. For patients with vault recurrence alone and no previous radiotherapy, the 2 and 5year overall survival was 90 % and 64% whiles that for pelvic recurrence was 48% and 14%. In a retrospective analysis of the PORTEC1 study[68], 5-year OS after vaginal recurrence was 70% in the patients that did not receive adjuvant RT. Salvage rate for patients with isolated vaginal recurrence is excellent but quite poor for those with pelvic recurrence as has been observed in this and other international studies[85]. There is therefore the need to identify subgroups who may benefit from the addition of EBRT to VBT. Patients with distance recurrence had the poorest survival of 42% at 2 years and 10% at 5 years, (P – value: 0.007). The development of distant metastases (lung, liver, bone metastases, brain and supra-diaphragmatic nodal metastases), according to several investigators, results in a considerable reduction in overall survival.[18,67,68,112]

A univariate analysis to determine the association between clinicopathological factors (age, stage, grade, lymphovascular invasion and histological type of endometrial cancer) and recurrence showed that LVSI was the only factor associated with recurrence in this cohort of patients. Lymphovascular space invasion can be defined as the presence of tumor cells in endothelial-lined spaces within the uterine wall outside the main tumor and an independent poor prognostic factor in early-stage endometrial cancer due to its association with nodal metastasis and disease recurrence in some studies[119]. There is therefore a possible correlation between this peculiar finding, the high lymph node positivity rate, as well as the high rate of pelvic and distance recurrence that was observed in this study. LVSI may be a more potent prognostic marker than grade and histological subtype, despite the fact that its presence does not always imply positive lymph nodes.[18,120] Tumor stage, increasing age, grade, myometrial invasion, lymphovascular space

invasion (LVSI) and high-risk histological type, are all traditional risk factors which have been linked to a higher risk of recurrence and nodal metastasis [18,68,69]. Age is a critical factor in risk assessment for both GOG and PORTEC risk stratification systems. In this study however, age, grade, and histology were not associated with recurrence, highlighting the need for more discriminating risk stratification system.

A Cox regression model was used to determine the clinical-pathologic factors associated with disease- free and overall survival. FIGO stage, histological grade and histological type were associated with survival.

Steiner et al.[121] found that histopathologic tumor type was an independent predictive factor for recurrence-free survival and mortality in a group of 181 women with endometrial cancer. Patients with adenocarcinoma had a considerably higher overall survival and recurrence-free survival than patients with other tumor forms, according to the investigators (papillary, clear-cell carcinoma, and others)

The most important predictive factor for endometrial cancer is surgical stage. In the GOG 33 trial, researchers looked at surgical and pathologic characteristics linked to lymph node involvement, extrauterine disease, and recurrence in clinical early-stage disease. In a multivariate analysis, lymph node metastasis was linked to the depth of myometrial invasion and extrauterine pathology. 51 In individuals with early-stage endometrial cancer, the degree of myometrial invasion was one of the most important predictive variables for recurrence.[122,123] Recurrence was also linked to the presence of lymph nodes in the pelvis and para-aortic region, which was linked to extrauterine metastasis to the cervix, adnexa, and peritoneum. These findings highlight the significance of surgical staging and prognostic grouping in order to give appropriate adjuvant treatment.

In endometrial cancer, the degree of tumor differentiation has been demonstrated to impact survival. Because of the strong association with other factors, determining the influence of this component as an independent prognostic variable is difficult. Poorly differentiated tumors had a higher probability of myometrial invasion and, as a result, lymph node metastasis, according to Creasman et al.[49] In an analysis of 111 endometrial cancer stage 1 surgical specimens, Hanson et

al[51], found a strong correlation between poorly differentiated tumours, Lymphovascular space invasion, deep myometrial penetration and malignant peritoneal cytology.

The sole demographic variable related with overall survival, according to a Cox regression analysis of the data, was marital status. Although there have been well-documented links between the presence of nurturing and supportive relationships and a variety of health outcomes,[124-126] it is uncertain whether cancer patient mortality is linked to social network factors such marital status. Seven research found a beneficial association between social activity and/or social support and cancer patient survival, according to a qualitative review. The apparent link between social network indicators and cancer patient mortality has elicited a number of plausible interpretations.

Social network effects could be biologically mediated, particularly through neuroendocrine or neuroimmune mechanisms. Social support, for example, may reduce or minimize the effects of stress-related endocrine alterations that could lead to tumor proliferation[127,128].

Again, one's social network may have an impact on one's health behavior. As a result of urging from social network members, married patients and those with a larger network may be detected earlier and hence have a better prognosis.

Third, people with richer social networks may have more or more dependable access to the health care system and its complications after being diagnosed with cancer. As a result, these patients may be more able to stick to their treatment regimens.

Finally, patients with better social networks may be more likely to receive vigorous, aggressive, active cancer treatment due to enhanced motivation as well as financial and psychological support. For example, married people have higher income and may have better access to cost intensive treatment. The above and many other reasons could be the result of the association between marital status and overall survival

CHAPTER SIX

6.0 Conclusions

Clinicopathological features and risk factors

Endometrial carcinoma ranked second most common gynaecological cancer seen between 2009 and 2018 with the mean age at presentation being 61.3 years. Majority were postmenopausal, married, literate and economically active women**.** Late age at menopause, high BMI, hypertension and diabetes were some of the common risk factors that we observed in the study population indicating common demographic and risk related features between this study population and other endometrial cancer women of different geographical regions.

Abnormal vaginal bleeding was the commonest presenting symptom majority of which was first reported at a health facility at least six months after the initial symptom. Endometrioid adenocarcinoma was the commonest histological subtype and less than fifty percent was FIGO stage 1 disease

.

Surgery

Lymph node dissection rate was noted to be 11% with an average of 13 pelvic and 6 para -aortic lymph doses sampled and a significantly high lymph node positivity rate of 62% in comparison to other international studies.

Treatment Outcome

Sample was grouped into low, low intermediate, high intermediate and high-risk groups according to the PORTEC risk stratification and overall survival for each risk group was similar in comparison to international studies. As was typical, overall survival declined with increasing risk. Disease- free survival was however, poorer compared to other international studies likely due to the high recurrence rates as well as the large number of patients defaulting adjuvant therapy.

Adjuvant treatment comprising of EBRT +/-VBT +/- chemotherapy resulted in a significantly improved DFS in intermediate, high-intermediate and high-risk groups. This was however not translated to improved overall survival due possibly to effective salvage therapy.

A major finding in this study was the significant effect of adjuvant external beam radiotherapy on the disease-free survival in the low intermediate risk population which is in stark

contrast to findings in other international studies. Although the numbers were small, almost half of patients in the low intermediate risk category who did not receive adjuvant external beam radiotherapy experienced recurrence most of which were pelvic.

Recurrence

There was a high recurrence rate of 35% among the whole sample of which most were pelvic recurrence. Aside low risk patients, pelvic recurrence dominate d in all the other risk groups. Patients with vault recurrence who had no previous radiotherapy had the best overall survival.

Factors associated with Survival

Lymphovascular invasion, histological type, FIGO stage and grade were associated with survival and marital status was the only socio-demographic factor associated with overall survival.

Recommendations

In view of the result of significantly reduced locoregional recurrences associated with EBRT, all patients with intermediate or high intermediate risk disease should be counselled to make an informed decision about EBRT.

In our setting, high consideration should be given to EBRT compared to VBT alone given the high incidence of pelvic recurrence vs vault.

Sub-specialization of gynae- oncology surgeons to carry out oncological procedures in order to increase patient load and improve skill.

The use of standard imaging such as CT scan and MRI both preoperatively and prior to adjuvant therapy will inform staging and the guide surgery and prevent geographical miss during radiotherapy.

Sentinel lymph node sampling is a viable option that can be explored in the management strategy of EC.

The incorporation of readily available molecular testing such as p53 overexpression, may be necessary to help identify patients who may benefit from radiotherapy.

Early presentation and diagnosis of patients especially in the African population with attempts to reduce the culture of late presentation and treatment defaults will significantly improve treatment outcomes.

Standardization of histopathologic reporting systems in accordance with internationally accepted protocols is required, as the absence of some critical information is a limitation in many retrospective studies. The establishment of a regulatory body may be necessary for the implementation of these standardized protocols. More importantly, this will help oncologists to make more objective decisions on adjuvant therapy not only in cases of endometrial cancer but in all other malignancies.

Collaborative efforts with other oncology centres in the country to prospectively assess the benefit of EBRT vs Brachytherapy in intermediate risk EC group will help validate the findings of this study and guide management.

The incorporation of readily available molecular testing such as p53 overexpression, may be necessary to help identify patients who may benefit from radiotherapy.

Limitations/Strengths

Limitations of our study as is common with all retrospective studies included inadequate record of socio-demographic and clinical data in the patients' folders, hence difficulty in obtaining enough information on aspects such as age at menarche and menopause and the presence or absence of hypertension and diabetes.

Another major limitation was the absence of some vital information in histopathology reports such as grade and the presence of or absence of lymphovascular space invasion making risk stratification difficult.

Patients were not matched for baseline characteristics which may have been a confounding factor. Generalization of the finding of the study may be questioned because of lack of randomization.

Treating clinician bias cannot be underestimated. Choice of treatment are influenced by several factors including both patient and doctor preferences. The choice of offering EBRT alone to specific risk group such as intermediate risk was solely dependent on attending physicians preference.

The purposive sampling method used for data collection could have led to bias since data collection was based on the judgement of the researcher and objectives of the study. As is common with this non probability sampling, criticism could arise concerning inferences made from the result of the study.

Thirty- four percent of patients were lost to follow up and there was no response in 9% of patients called to determine their survival status. This was an obvious limitation of the study.

With so much conflicting data on the management of women with endometrial cancer especially in the choice of adjuvant therapy, this study holds the strength of adding information to published data by proposing the hypothesis that, adjuvant external beam radiotherapy may be beneficial to a subset of patients with intermediate risk disease. This could be investigated in a large prospective trial using newer treatment techniques

REFERRENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424.
2. Missaoui N, Jaidene L, Abdelkader AB, Abdelkrim SB, Beizig N, et al. Cancer of corpus uteri in Tunisia: epidemiological and clinicopathological features. Asian Pac J Cancer Prev. 2011 Jan 1;12(2):461-4.
3. Ugwu EO, Iferikigwe ES, Okeke TC, Ugwu AO, Okezie OA, et al. Pattern of gynaecological cancers in University of Nigeria Teaching Hospital, Enugu, south eastern Nigeria. Nigerian journal of medicine: journal of the National Association of Resident Doctors of Nigeria. 2011;20(2):266-9.
4. Nkyekyer K. Pattern of gynaecological cancers in Ghana. East African medical journal. 2000;77(10).
5. Muhammad AA, Adekunle OO, Modupeola SO, Muhammad U, Zulaiha S,et al. A. A diary of endometrial malignancies in Zaria, Northern Nigeria. Sub-Saharan African Journal of Medicine. 2017 Apr 1;4(2):43.
6. Rauh-Hain JA, Del Carmen MG. Endometrial stromal sarcoma: a systematic review. Obstetrics & Gynecology. 2013 Sep 1;122(3):676-83
7. Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, et al. Factors associated with Type I and Type II endometrial cancer. Cancer Causes & Control. 2010 Nov 1;21(11):1851-6.
8. Iqbal J, Ginsburg OM, Wijeratne TD, Howell A, Evans G, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. Cancer treatment reviews. 2012 Jun 1;38(4):318-28.
9. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet. 2008 Feb 16;371(9612):569-78..
10. Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. British journal of cancer. 2008 May;98(9):1582-5.

11. Bendifallah S, Ouldamer L, Lavoue V, et al. Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO Consensus Conference risk groups: results from the FRANCOGYN study Group. Gynecol Oncol. 2017;144: 107Y112
12. . Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101:520Y529.
13. Del Carmen MG, Boruta DM, Schorge JO. Recurrent endometrial cancer. Clin Obstet Gynecol. 2011;54:266Y277
14. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet*. (2016) 387:1094–108
15. Evans T, Sany O, Pearmain P, Ganesan R, Blann A, et al. Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. British journal of cancer. 2011 Apr;104(9):1505-10.
16. Siegel R, Naishadham D, Jemal A. Global cancer statistics. CA Cancer J Clin. 2013;63(1):11-30.
17. Sud S, Holmes J, Eblan M, Chen R, Jones E. Clinical characteristics associated with racial analysis. Gynecologic oncology. 2018 Feb 1;148(2):349-56.
18. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynaecologic Oncology Group study. Gynaecologic oncology. 2004 Mar 1;92(3):744-51.
19. Meissner WA, Sommers SC, Sherman G. Endometrial hyperplasia, endometrial carcinoma, and endometriosis produced experimentally by oestrogen. Cancer. 1957 May;10(3):500-9.
20. Mansell H, Hertig AT. Granulosa-theca cell tumours and endometrial carcinoma: A study of their relationship and a survey of 80 cases. Obstetrics & Gynaecology. 1955 Oct 1;6(4):385-94.
21. Camlibel AR. Postmenopausal bleeding: First steps in the workup. the journal of family practice. 2012 Oct;61(10).

22. Missaoui N, Jaidene L, Abdelkader AB, Abdelkrim SB, Beizig N, et al. Cancer of corpus uteri in Tunisia: epidemiological and clinicopathological features. Asian Pac J Cancer Prev. 2011 Jan 1;12(2):461-4.
23. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, et al. Endometrial cancer. The Lancet. 2005 Aug 6;366(9484):491-505.
24. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynaecologic oncology. 2014 Oct 1;135(1):163-71.
25. Duong LM, Wilson RJ, Ajani UA, Singh SD, Eheman CR. Trends in endometrial cancer incidence rates in the United States, 1999–2006. Journal of women's health. 2011 Aug 1;20(8):1157-63.
26. Buchanan EM, Weinstein LC, Hillson C. Endometrial cancer. American family physician. 2009 Nov 15;80(10):1075-80.
27. Manchana T, Khemapech N. Endometrial adenocarcinoma in young Thai women. Asian Pac J Cancer Prev. 2008 Jan 1;9(2):283-6.
28. Farley J, Risinger JI, Rose GS, Maxwell GL. Racial disparities in blacks with gynaecologic cancers. Cancer. 2007 Jul 15;110(2):234-43
29. Reis N, Beji NK. Risk factors for endometrial cancer in Turkish women: results from a hospital-based case–control study. European Journal of Oncology Nursing. 2009 Apr 1;13(2):122-7.
30. Setiawan VW, Pike MC, Kolonel LN, Nomura AM, Goodman MT, et al. Racial/ethnic differences in endometrial cancer risk: the multi-ethnic cohort study. American journal of epidemiology. 2007 Feb 1;165(3):262-70.
31. Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. British journal of cancer. 2008 May;98(9):1582-5.
32. Key T, Appleby P, Barnes I, Reeves G. Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal

women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002 Apr 17;94(8):606-16.

33. Xu WH, Matthews CE, Xiang YB, Zheng W, Ruan ZX, et al. Effect of adiposity and fat distribution on endometrial cancer risk in Shanghai women. American journal of epidemiology. 2005 May 15;161(10):939-47.
34. Charneco E, Ortiz AP, Venegas-Ríos HL, Romaguera J, Umpierre S. Clinic-based case-control study of the association between body mass index and endometrial cancer in Puerto Rican women. Puerto Rico health sciences journal. 2010 Sep;29(3):272
35. Thomas CC, Wingo PA, Dolan MS, Lee NC, Richardson LC. Endometrial cancer risk among younger, overweight women. Obstetrics & Gynaecology. 2009 Jul 1;114(1):22-7.
36. Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA. Weight change and risk of endometrial cancer. International journal of epidemiology. 2006 Feb 1;35(1):151-8.
37. Serin IS, Ozçelik B, Basbug M, Ozsahin O, Yilmazsoy A,et al. Effects of hypertension and obesity on endometrial thickness. European Journal of Obstetrics & Gynaecology and Reproductive Biology. 2003 Jul 1;109(1):72-5.
38. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. American journal of obstetrics and gynaecology. 1992 Nov 1;167(5):1317-25.
39. Saltzman BS, Doherty JA, Hill DA, Beresford SA, Voigt LF, et al. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. American journal of epidemiology. 2008 Mar 1;167(5):607-14.
40. Zendehdel K, Nyrén O, Östenson CG, Adami HO, Ekbom A, et al. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. Journal of the National Cancer Institute. 2003 Dec 3;95(23):1797-800
41. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiology and Prevention Biomarkers. 2007 Feb 1;16(2):276-80.
42. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynaecologic oncology. 1983 Feb 1;15(1):10-7.

43. Levine DA, Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May;497(7447):67-73.
44. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, et al Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Modern pathology. 2015 Jun;28(6):836-44.
45. Talhouk A, McConechy MK, Leung S, Yang W, Lum A et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017 Mar 1;123(5):802-813.
46. Billingsley CC, Cohn DE, Mutch DG, Stephens JA, Suarez AA, et al. Polymerase ε (POLE) mutations in endometrial cancer: Clinical outcomes and implications for L ynch syndrome testing. Cancer. 2015 Feb 1;121(3):386-94.
47. Talhouk A, Hoang LN, McConechy MK, Nakonechny Q, Leo J, et al. Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: earlier prognostic information to guide treatment. Gynaecologic oncology. 2016 Oct 1;143(1):46-53.
48. Schultheis AM, Martelotto LG, De Filippo MR, Piscuoglio S, Ng CK, et al. TP53 mutational spectrum in endometrioid and serous endometrial cancers. International journal of gynaecological pathology: official journal of the International Society of Gynaecological Pathologists. 2016 Jul;35(4):289.
49. Creasman WT. Announcement FIGO stages: 1988 revisions. Gynecol Oncol. 1989;35:125-7.
50. Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstetrics and Gynaecology. 1984 Jun;63(6):825-32.
51. Hanson WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynaecologic Oncology Group study. Cancer. 1987 Oct 15;60(S8):2035-41.
52. Mutch DG. The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas. Gynaecologic oncology. 2009 Dec 1;115(3):325-8.
53. Metindir J, Dilek GB. The role of omentectomy during the surgical staging in patients with clinical stage I endometrioid adenocarcinoma. Journal of cancer research and clinical oncology. 2008 Oct 1;134(10):1067-70.

54. Gehrig PA, Van Le L, Fowler WC. The role of omentectomy during the surgical staging of uterine serous carcinoma. International Journal of Gynaecologic Cancer. 2003 Feb 1;13(2):212-5.
55. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network. 2018 Feb 1;16(2):170-99.
56. . European Society for Medical Oncology (EMSO). ESMO Guidelines. esmo.org/ guidelines. Accessed January 21. 2019
57. Rungruang B, Olawaiye AB. Comprehensive surgical staging for endometrial cancer. Reviews in Obstetrics and Gynaecology. 2012;5(1):28.
58. May K, Bryant A, Dickinson HO, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane database of systematic reviews. 2010(1).
59. Arango HA, Hoffman MS, Roberts WS, DeCesare SL, Fiorica JV, et al. Accuracy of lymph node palpation to determine need for lymphadenectomy in gynaecologic malignancies. Obstetrics & Gynaecology. 2000 Apr 1;95(4):553-6.
60. Case AS, Rocconi RP, Straughn JM, Conner M, Novak L, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. Obstetrics & Gynaecology. 2006 Dec 1;108(6):1375-9.
61. Panici PB, Basile S, Maneschi F, Lissoni AA, Signorelli M, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. JNCI: Journal of the National Cancer Institute. 2008 Dec 3;100(23):1707-16.
62. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet (London, England). 2008 Dec 16;373(9658):125-36.
63. Kang S, Yoo HJ, Hwang JH, Lim MC, Seo SS, et al. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. Gynaecologic oncology. 2011 Dec 1;123(3):522-7.

64. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, et alF. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. The Lancet Oncology. 2017 Mar 1;18(3):384-92.
65. Sorbe B, Nordström B, Mäenpää J, Kuhelj J, Kuhelj D, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. International Journal of Gynaecologic Cancer. 2009 Jul 1;19(5):873-8.
66. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynaecologic Oncology Group study. Gynaecologic oncology. 2004 Mar 1;92(3):744-51.
67. Aalders J, Abeler VE, Kolstad P, Onsrud MA. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstetrics and gynaecology. 1980 Oct;56(4):419-27.
68. Creutzberg CL, Nout RA, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. International Journal of Radiation Oncology* Biology* Physics. 2011 Nov 15;81(4):e631-8.
69. Nout RA, Smit VT, Putter H, Juergenliemk-Schulz IM, Jobsen JJ, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. The Lancet. 2010 Mar 6;375(9717):816-23.
70. ASTEC T. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN. 5 randomised trials): pooled trial results, systematic review, and meta-analysis. The Lancet. 2009 Jan 10;373(9658):137-46.
71. Sorbe BG, Horvath G, Andersson H, Boman K, Lundgren C, et al. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma: a prospective, randomized study—quality-of-life analysis. International Journal of Gynaecologic Cancer. 2012 Sep 1;22(7):1281-8.
72. Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with

intermediate-and high-risk endometrial cancer: a Japanese Gynaecologic Oncology Group study. Gynaecologic oncology. 2008 Jan 1;108(1):226-33.

73. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynaecologic Oncology Group Study. Journal of clinical oncology. 2006 Jan 1;24(1):36-44.
74. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. British journal of cancer. 2006 Aug;95(3):266-71.
75. Randall ME, Filiaci V, McMeekin D, Yashar CM, Mannel R, et al. A phase 3 trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: a Gynaecology Oncology Group study. International Journal of Radiation Oncology• Biology• Physics. 2017 Dec 1;99(5):1313.
76. Hogberg T, Signorelli M, de Oliveria CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer— results from two randomised studies. *Eur J Cancer*. 2010;46:2422-2431.
77. Einstein MH, Frimer M, Kuo DY, et al. Phase II trial of adjuvant pelvic radiation "sandwiched" between combination paclitaxel and carboplatin in women with uterine papillary serous carcinoma. *Gynecol Oncol.* 2012;124:21-25.
78. Klopp AH, Yeung AR, Deshmukh S, et al. A phase III randomized trial comparing patient reported toxicity and quality of life (QOL) during pelvic intensity modulated radiation therapy as compared with conventional radiation therapy [abstract]. *Int J Radiat Oncol Biol Phys.* 2016;95(2 suppl):S3.
79. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2018;19:295-309.
80. Matei D, Filiaci VL, Randall M, et al. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs carboplatin and

paclitaxel for optimally debulked, advanced endometrial carcinoma [abstract]. *J Clin Oncol.* 2017;35(15 suppl):5505.

81. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. *Gynecol Oncol*. 2010;118:14–18.
82. Carey MS, O'Connell GJ, Johanson CR, Goodyear MD, Murphy KJ, et al. Good outcome associated with a standardized treatment protocol using selective postoperative radiation in patients with clinical stage I adenocarcinoma of the endometrium. *Gynecol Oncol*. 1995;57:138–144.
83. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, et al. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary?. American journal of obstetrics and gynecology. 2000 Jun 1;182(6):1506-19.
84. Rauh-Hain JA, Del Carmen MG. Treatment for advanced and recurrent endometrial carcinoma: combined modalities. Oncologist. 2010;15:852Y861.
85. Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis. J Natl Cancer Inst. 2012;104:1625–1634.
86. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol BiolPhys. 2003;56:1366–1372.
87. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: Results of salvage radiotherapy. Int J Radiat Oncol Biol Phys. 2000;48:405–413.
88. Ueda SM, Kapp DS, Cheung MK, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol. 2008;198:218e1–218e6.
89. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94:642–646
90. Barakat RR, Goldman NA, Patel DA, et al. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol. 1999;75:99–102

91. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. Gynecol Oncol. 2000;77:66–72.
92. Sorosky JI. Endometrial cancer. Obstet Gynecol 2008; 111:436–447.
93. Manchana T, Khemapech N. Endometrial adenocarcinoma in young Thai women. Asian Pac J Cnacer Prev 2008; 9:283–286.
94. Fujita M, Tase T, Kakugawa Y, et al. Smoking, earlier menarche and low parity as independent risk factors for gynecologic cancers in Japanese : a case-control study. Tohoku J Exp Med 2008; 216:297–307.
95. **S**oliman PT, Oh JC, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol 2005; 105:575–580
96. Adadevoh SW, Agble TK, Hobbs C, Elkins TE. Menarcheal age in Ghanaian school girls. Int J Gynaecol Obstet. 1989 Sep;30(1):63-8.
97. Aryeetey R, Ashinyo A, Adjuik M. Age of menarche among basic level school girls in Medina, Accra. Afr J Reprod Health. 2011 Sep;15(3):103-10.
98. Kwawukume EY, Ghosh TS, Wilson JB. Menopausal age of Ghanaian women. Int J Gynaecol Obstet. 1993 Feb;40(2):151-5
99. Gavrilyuk, O., Braaten, T., Weiderpass, E., Licaj, I. and Lund, E., 2018. Lifetime number of years of menstruation as a risk index for postmenopausal endometrial cancer in the Norwegian Women and Cancer Study. *Acta obstetricia et gynecologica Scandinavica*, *97*(10), pp.1168-1177
100. Dossus L, Allen N, Kaaks R, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;127:442-451
101. Wernli KJ, Ray RM, Gao DL, De Roos AJ, Checkoway H, Thomas DB. Menstrual and reproductive factors in relation to risk of endometrial cancer in Chinese women. Cancer Causes Control. 2006;17:949-955.
102. Benkeser RM, Biritwum R, Hill AG. Prevalence of overweight and obesity and perception of healthy and desirable body size in urban, Ghanaian women. Ghana Med J. 2012 ;46(2):66-75.

103. Ghana Health Service. *The Health Sector in Ghana: Facts and Figures 2018*. Accra, Ghana: Ghana Health Service, 2018.

104. Bosu WK, Bosu DK. Prevalence, awareness and control of hypertension in Ghana: A systematic review and meta-analysis. PloS one. 2021:16(3):e0248137

105. Danquah I, Bedu-Addo G, Terpe KJ, Micah F, Amoako YA, Awuku YA, Dietz E, van der Giet M, Spranger J, Mockenhaupt FP. Diabetes mellitus type 2 in urban Ghana: characteristics and associated factors. *BMC Public Health.* 2012;**12**:210.

106. Saeed BI, Abdul-Aziz AR, Nguah SB, Zhao X. The effect of socio-economic predictors of chronic diseases in Ghana: results of a nationwide survey. *Global J Health Sci.* 2013;**5**(5):115–123.

107. Amoah AG, Owusu SK, Adjei S. Diabetes in Ghana: a community based prevalence study in Greater Accra. *Diabetes Res Clin Pract.* 2002;**56**(3):197–205.

108. Burbos N, Musonda P, Duncan TJ et al. Estimating the risk of endometrial cancer in symptomatic postmenopausal women: a novel clinical prediction model based on patients' characteristics. International Journal of Gynecologic Cancer. 2011 Apr 1;21(3).

109. Yarney J, Donkor A, Opoku S, Yarney Let al. Characteristics of users and implications for the use of complimentary and alternative medicines in Ghanaian cancer patients undergoing radiotherapy and chemotherapy: a cross sectional study. BMC complimentary and alternative medicine. 2013; 13-16.

110. Muhammad AA, Adekunle OO, Modupeola SO et al. A. A diary of endometrial malignancies in Zaria, Northern Nigeria. Sub-Saharan African Journal of Medicine. 2017 Apr 1;4(2):43.

111. Altekruse S, Kosary C, Krapcho M et al., *SEER Cancer Statistics Review, 1975-2007*, National Cancer Institute, Bethseda, MD,USA,2010.

112. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wa´rla´m-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E, Beerman H, van Lent M Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355: 1404–1411.

113. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010; 375: 1165–1172.

114. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, Sessa C. ESMO Guidelines Working Group Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(Suppl 6): vi33–vi38.

115. Bendifallah S, Canlorbe G, Raimond E, Hudry D, Coutant C, Graesslin O, Touboul C, Huguet F, Cortez A, Daraı¨ E, Ballester M. A clue towards improving the European Society of Medical Oncology risk group classification in apparent early stage endometrial cancer? Impact of lymphovascular space invasion. Br J Cancer 2014; 110(11): 2640–2646

116. Cosgrove CM, Tritchler DL, Cohn DE, *et al.*: An NRG Oncology/GOG study of molecular classification for risk prediction in endometrioid endometrial cancer. *Gynaec Oncol.* 2018; 148(1): 174–80.

117. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium. A clinical and histopathological study of 379 patients. *Gynecol Oncol.* 1984;**17**:85–103.

118. Sohaib SA, Houghton SL, Rexnek RH, et al. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. *Clin Radiol.* 2007;**62**:28–34.

119. Guntupalli SR, Zighelboim I, Kizer NT, Zhang Q, Powell MA, Thaker PH et al Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol 2012:124:31–35

120. Narayan K, Khaw P, Bernshaw D, et al. Prognostic significance of lymphovascular space invasion and nodal involvement in intermediate- and high-risk endometrial cancer patients treated with curative intent using surgery and adjuvant radiotherapy. Int J Gynecol Cancer. 2012;22:260–6

121. Steiner E, Eicher O, Sagemüller J, Schmidt M, Pilch H et al. Multivariate independent prognostic factors in endometrial carcinoma: a clinicopathologic study in 181 patients: 10 years experience at the Department of Obstetrics and Gynecology of the Mainz University. Int J Gynecol Cancer. 2003 13(2):197-203

122. Morrow CP, Bundy BN, Kurman RJ, Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynaecology Oncology group study. Gynaecol Oncol. 1991: 40, 55-65.

123. Lurain JR. Rice BL, Rademaker AW, Prognostic factors associated with recurrence in clinical stage 1adenocarcinoma of the endometrium. Obstet. Gynecol. 1991: 78, 63-69.

124. Berkman LF. The role of social relations in health promotion. *PsychosomMed.* 1995;57:245–54.

125. House JS, Landis KR, Umberson D. Social relationships and health. *Science.* 1988;241:540–5.

126. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychol Bull.* 1996;119:488–531

127. Spiegel D. Psychosocial intervention in cancer. *J Nat Cancer Inst.* 1993;85:1198–205.

128. Levy SM, Herberman RB, Whiteside T, Sanzo K, Lee J, Kirkwood J. Perceived social support and tumor estrogen/progesterone receptor status as predictors of natural killer cell activity in breast cancer patients. *Psychosom Med.* 1990;52:73–85.

129. Adreano A, Rechichi G, Rebora P, et al. MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis, *Eur Radiol* 2014;24(6):1327-1338

130. Bolloneni VR, Ytre-Hauge S, Bollineni-Balabay O, et al. High diagnostic value of 18F-FDG PET/CT in endometrial cancer:systematic review and meta-analysis of the literature. *J Nucl Med* 2016;57(6):879-885

APPENDIX

DATA COLLECTION FORM

TOPIC: ENDOMETRIAL CANCER IN GHANA – A 10 YEAR REVIEW OF CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOMES

DEMOGRAPHIC VARIABLES

1. Folder Number**.....**
2. Date of 1st Attendance……
3. Age**.....**
4. Occupation**.....**
5. Residence**.....**
6. Tribe**.....**
7. Telephone Number**.....**

CLINICAL VARIABLES

8. Weight (Kg)**……**
9. Height(cm)**……**
10. Age at Menaerche**……..**

11. Age at Menopause**…….**

12. Number of pregnancies**…….**

13. Number of children**……**

14. Date of Histological diagnosis**…….**

15. Histology**…….**

16. Grade**……**

17. Lymphovascular invasion**…….**

18. Stage**……**

TREATMENT VARIABLES

19. Type of surgery**……..**

20. Lymphadenectomy?

Yes**……..** No**……..**

21. If Yes, Number and site of Lymph nodes**.....**

22. Date of surgery**……..**

23. Performance status (Tick)

ECOG 1……

ECOG 2……

ECOG 3.....

ECOG 4……

ECOG 5……

24. Treatment plan

Observation……..

Adjuvant Radiotherapy……..……..

Adjuvant chemotherapy……..…….

Adjuvant Radiotherapy and chemotherapy……..

25. Type of Chemotherapy……

26. Number of cycles.....

27. Start date..... End date……

28. Radiotherapy dose……...

29. Number of fractions…….

30. Start date……. End date…….

31. Brachytherapy

Yes**.....** No**……..**

32. Type of Brachytherapy

LDR**.....** HDR**……..**

33. Date of brachytherapy**…….**

34. Dose and fraction of brachytherapy**.....**

FOLLOW UP VARIABLES

35. Recurrence

Yes**.....** No**.....**

36. Site of recurrence**.....**

37. Date of recurrence**.....**

38. Date last seen**…….**

39. Current condition

Alive**……** Dead**.....**

40. Date of death**……..**

In case of reply the number
And the date of this
Letter should be quoted

My Ref. No. KBTH/MD/Pg/3121

Your Ref. No......

KORLE BU TEACHING HOSI
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-(
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

4th June, 2021

DR MARY-ANN DADZIE
NATIONAL CENTRE FOR RATIOTHERAPY AND
NUCLEAR MEDICINE
KORLE BU TEACHING HOSPITAL
P.O.BOX KB369 KORLE BU, ACCRA

SCIENTIFIC AND TECHNICAL COMMITTEE APPROVAL
PROTOCOL IDENTIFICATION NUMBER: KBTH-STC 00084/2021

The Korle Bu Teaching Hospital Scientific and Technical Committee (KBTH-STC), on 4th June, 2021 approved your submitted study protocol.

TITLE OF PROTOCOL: "Endometrial Cancer in Ghana – A 10 Year Review of Clinicopathological Features and Treatment Outcome"

PRINCIPAL INVESTIGATOR: Dr Mary-Ann Dadzie

This approval requires that you **forward your approved document to Korle Bu Teaching Hospital –Institutional Review Board (KBTH-IRB) for the ethical aspect of the proposal to be assessed before the project can be initiated.**

This STC approval is valid till 30th December, 2021
You may, however, request extension of the approval period, or renewal as the case may be, should the study extend beyond the stated period.

Upon completion, you are required to submit a final report on the study to the STC. This is to enable the STC ensure among others that, the project has been implemented as per the approved protocol. You are also required to inform the KBTH-STC and Research Directorate of any publications that may emanate from the research findings.

Kindly note that, should the need arise, the KBTH-STC or IRB may institute appropriate measures to satisfy itself that study is being conducted according to the highest scientific and ethical standards.

Please note that any modification to the study protocol without Scientific Technical Committee (STC) approval renders this approval invalid.

Sincere regards,

Prof. G. Obeng Adjei
Chairman, KBTH-STC

Cc: The Chairman, KBTH-IRB

In case of reply the number
And the date of this
Letter should be quoted

My Ref. No. KBTH/MD/63/21

Your Ref. No......

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-6
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

23rd June, 2021

DR MARY-ANN DADZIE
NATIONAL CENTRE FOR RADIOTHERAPY AND NUCLEAR MEDICINE
KORLE BU TEACHING HOSPITAL
P.O.BOX KB369 KORLE BU, ACCRA

INSTITUTIONAL APPROVAL: KORLE BU TEACHING HOSPITAL-SCIENTIFIC AND TECHNICAL COMMITTEE/INSTITUTIONAL REVIEW BOARD (KBTH-STC/IRB/00084/2021

Following approval of your study entitled "Endometrial Cancer in Ghana – A 10 Year Review of Clinicopathological Features and Treatment Outcome" by the Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board.

I am pleased to inform you that institutional approval has been granted for the conduct of your study in Korle Bu Teaching Hospital.

Please contact the Head of Department to discuss the commencement date of the study.

Please note that, this institutional approval is rendered invalid if the terms of the Institutional Reviewed Board/Scientific and Technical Committee approval are violated.

Sincere regards,

Dr. Ali Samba
Director of Medical Affairs
For: Chief Executive

MEDICAL DIRECTORATE
KORLE BU TEACHING HOSPITAL

23rd June, 2021

THE HEAD
NATIONAL CENTRE FOR RADIOTHERAPY AND NUCLEAR MEDICINE
KORLE BU TEACHING HOSPITAL
P.O.BOX KB369 KORLE BU, ACCRA

LETTER OF INTRODUCTION – DR MARY-ANN DADZIE
"ENDOMETRIAL CANCER IN GHANA - A 10 YEAR REVIEW OF CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOME"

I have the pleasure to introduce to you the above named Investigator from National Centre for Radiotherapy and Nuclear Medicine, Korle Bu, Accra. Dr Mary-Ann Dadzie sought and has been granted approval to conduct a study entitled "Endometrial Cancer in Ghana – A 10 Year Review of Clinicopathological Features and Treatment Outcome".

She is to contact you to discuss the commencement date of the study.

Please verify her identity with a Government issued National ID card and accord her the needed assistance.

Attached is the Scientific and Technical Committee and Institutional Review Board approval, which specifies the terms.

Sincere regards,

Dr. Ali Samba
Director of Medical Affairs
For: Chief Executive

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No. KBTH/MD/03124
Your Ref. No.....

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-6
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

23rd June, 2021

DR MARY-ANN DADZIE
NATIONAL CENTRE FOR RADIOTHERAPY AND NUCLEAR MEDICINE
KORLE BU TEACHING HOSPITAL
P.O.BOX KB369 KORLE BU, ACCRA

ENDOMETRIAL CANCER IN GHANA - A 10 YEAR REVIEW OF CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOME

KBTH-IRB /00084/2021

INVESTIGATOR: Dr Mary-Ann Dadzie

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled: "Endometrial Cancer in Ghana – A 10 Year Review of Clinicopathological Features and Treatment Outcome"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 30th April, 2022. You are to submit annual report for continuing review.

Sincere regards,

DR. DANIEL ANKRAH
VICE CHAIR (KBTH-IRB)
FOR: CHAIR (KBTH-IRB

Cc: The Chief Executive Officer, KBTH
The Director of Medical Affairs, KBTH