ENDOMETRIAL CARCINOMA REVIEW: A 10-YEAR HOSPITAL UNIVERSITI SAINS MALAYSIA EXPERIENCE (JANUARY 2002 – DECEMBER 2011)

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This work is dedicated to all my patients; past, present and future.

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ABBREVIATIONS AND GLOSSARY

adj	Adjuvant
ASR	Age standardise incidence rate
BMI	Body mass index
BSO	Bilateral salphingo-oopherectomy
CA 125	Cancer antigen 125
CI	Confidence interval
COCP	Combined oral contraceptive pill
CR	Crude incidence rate
CT	Chemotherapy
CT scan	Computed tomography scan
df	Degree of freedom
DM	Diabetes mellitus
FIGO	International Federation of Gynaecology and Obstetrics
G	Grade
HR	Hazard ratio
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
HPE	Histopathological examination
HPL	Hyperlipidaemia
HPT	Hypertension
HT	Hormonal therapy
ICD	International Classification of Diseases
ICU	Intensive care unit
kg	Kilogram
m	Meter
MRI	Magnetic resonance imaging
O&G	Obstetrics & Gynaecology
p53	Tumour protein p53
PCOS	Polycystic ovarian syndrome
PTEN	Phosphatase and tensin homolog

SD	Standard deviation
WHO	World Health Organization

ABSTRAK (Malay version)

Topik:

Kajian kanser endometrium: Pengalaman 10 tahun di Hospital Universiti Sains Malaysia

(Januari 2002 - Disember 2011)

Objektif:

Kajian ini dijalankan untuk menentukan kelaziman, untuk menilai respons daripada semua kaedah rawatan, dan untuk menentukan kadar insiden kes berulang, serta untuk menentukan kadar kelansungan hidup pesakit-pesakit kes kanser endometrium yang telah dirawat di Hospital Universiti Sains Malaysia dari Januari 2002 hingga Disember 2011.

Metodologi:

Ini adalah satu kajian retrospektif , yang mana ia dijalankan secara mengkaji semula rekod perubatan pesakit dengan diagnosis seperti "kanser endometrium , karsinoma endometrium, kanser rahim dan kanser corpus uteri". Maklumat relevan yang telah diperolehi kemudian dicatatkan, seterusnya dianalisis menggunakan statistik deskriptif. Untuk analisis purata yang bermakna bagi sesetengah faktor yang berkaitan, ujian satu sampel t telah digunakan. Untuk analisis kelansungan hidup, model univarian ringkas dan multivarian regresi Cox telah digunakan.

Hasil:

Sebanyak 56 kes telah dimasukkan ke dalam kajian ini. Majoriti pesakit adalah kaum Melayu (89.3%), dan kaum Cina (8.9%). Faktor-faktor yang berkaitan dengan insiden kes kanser endometrium adalah umur menopaus, dengan puncak insiden berlaku di kalangan pesakit dalam lingkungan umur 50-55, dengan purata umur 54.3 (SD 11.77, p = 0.036), sejarah kemandulan dan bilangan kelahiran rendah (purata 2.75, SD 2.63, p = < 0.001), indeks jisim badan (BMI) tinggi dengan purata BMI 27.2 (SD 5.43, p = 0.003), dan mereka yang mempunyai tekanan darah tinggi (53.6 %) serta kencing manis (21.4 %). Hampir semua pesakit hadir dengan gejala (96.4 %), dengan gejala utama adalah pendarahan faraj yang abnormal daripada 91.1 % pesakit, dan sakit abdomen daripada 19.6 % pesakit. Walau bagaimanapun, majoriti pesakit (55.4%) tidak mempunyai sebarang tanda fizikal daripada hasil pemeriksaan. Untuk pesakit yang selebihnya , penemuan fizikal yang utama adalah kehadiran ketulan abdomen (39.3%). Ultrasound adalah jenis pengimejan yang paling utama. Ciri-ciri utama dari hasil ultrasound ialah ketebalan endometrium yang tidak normal dengan ketebalan sama atau lebih daripada 5 mm (85.7%), dan rahim besar (48.2%). Ujian diagnostik yang menjadi pilihan utama ialah adalah pensampelan pipelle (42.9%), diikuti oleh histeroskopi beserta biopsi tisu (28.6%). Apabila penyakit ini ditahapkan , majoriti pesakit berada di tahap I (67.9 %). Untuk tahap lain , 8.9 % daripada pesakit berada di tahap II , 19.7 % pula berada di tahap III dan 3.6% berada di tahap IV. Jenis histologi yang terbanyak ialah daripada jenis ‘endometrioid adenocarcinoma’ serta sub-jenisnya iaitu sebanyak 87.5 %. Lain-lain jenis histologi adalah agak jarang berlaku , dengan jenis ‘serous cell’ hanya sebanyak 3.6%, jenis ‘clear cell’ hanya sebanyak 3.6%, jenis ‘mixed adenocarcinoma’ hanya sebanyak 3.6%, serta jenis ‘undifferentiated cell’ hanya daripada 1.8%. Dalam segi gred histologi , kebanyakan tumor adalah dalam gred 1 (41.1 %) dan gred 2 (39.3 %), manakala hanya 19.6 % adalah gred 3. Jenis utama histologi tumor dengan gred 1 dan gred 2 adalah

daripada jenis ‘endometrioid adenocarcinoma’, sedangkan untuk gred 3 biasanya adalah daripada jenis ‘adenocarcinoma’ yang lain (‘serous cell’, ‘clear cell’, ‘mixed adenocarcinoma’ dan ‘undifferentiated cell’). Ketumbuhan jenis ‘endometrioid adenocarcinoma’ juga sering berlaku di tahap awal dan pada pesakit dilingkungan usia bawah 60. Untuk kaedah rawatan, semua pesakit telah menjalani pembedahan sepanjang rawatan. Majoriti pesakit menjalani pembedahan dengan rawatan susulan radioterapi (46.4 %), manakala 39.3% pesakit lagi hanya menjalani pembedahan sahaja. Bagi jenis pembedahan , jenis pembedahan utama ialah histerektomi ‘extrafacial’ beserta ‘bilateral salphingo – oopeherectomy’ (BSO)(46.4%), diikuti oleh histerektomi mudah beserta BSO (41.1 %). Walaupun dengan rawatan yang sesuai , masih berlaku kes berulang pada sebilangan kecil daripada pesakit, dan seterusnya kematian. 75.0 % daripada pesakit adalah bebas penyakit selepas 24 bulan, manakala selebihnya sebanyak 25.0 % mengalami kes berulang dalam tempoh kurang 24 bulan, dengan sebahagian besar daripada pesakit tersebut (12.5 %) mengalami kes berulang dalam tempoh kurang dari 6 bulan selepas rawatan. 80.4 % daripada pesakit masih hidup selepas 24 bulan selepas rawatan , manakala yang lain iaitu 19.6 % daripada pesakit pula meninggal dunia dalam masa kurang dari 24 bulan, dengan kadar kematian yang paling tinggi iaitu 12.5% meninggal dunia berlaku dalam tempoh kurang dari 6 bulan. Faktor penentuan paling bermakna ialah tahap penyakit (tahap III , p = 0.003 , HR diselaraskan 26.243) dan gred histologi (gred 3, p = 0.015 , HR diselaraskan 10.887). Kadar kelansungan hidup untuk tempoh 2 tahun ialah 97.4% bagi tahap I, 60.0 % bagi tahap II, 36.4 % untuk tahap III, dan 50.0 % bagi tahap IV.

Kesimpulan :

Walaupun kajian ini tidak berupaya untuk mengenalpasti kadar kelangsungan hidup bagi tempoh 5 tahun kerana keterbatasan kajian, namun begitu daripada kadar kelansungan hidup yang dinilai bagi tempoh 2 tahun ia berjaya menunjukkan ada pengaruh faktor penentuan yang kuat dari segi tahap dan gred penyakit.

ABSTRACT (English version)

Topic: Endometrial carcinoma review: A 10-year Hospital Universiti Sains Malaysia (HUSM) experience (January 2002 – December 2011)

Objective:

This study was conducted to determine the prevalence, and to evaluate the response of all treatment modalities, and to determine the incidence of recurrence, and to determine the survival rate of endometrial carcinoma cases that was managed in Hospital University Sains Malaysia from January 2002 until December 2011.

Methodology:

This is a retrospective study, which conducted by reviewing the patients' medical records with diagnosis of "endometrial cancer, endometrial carcinoma, or uterine cancer". Relevant information was obtained, recorded then analysed using descriptive statistics. The one sample t test was used to determine the significant mean for some of the associated factors. For survival analysis, simple univariate and multivariate Cox regression model was used.

Results:

A total of 56 cases were included in this study. Majority of the patients were Malays (89.3%), and Chinese (8.9%). The factors that associated incidence of endometrial carcinoma were postmenopausal age with peak incidence was in age group of 50-55 years, mean age 54.3 years (SD 11.77, p = 0.036), nulliparity and low parity (mean 2.75, SD 2.63, p = < 0.001), increase body mass index (BMI) with mean BMI 27.2 kg/m^2 (SD 5.43, p = 0.003) and those with underlying hypertension (53.6%) and diabetes mellitus (21.4%). Almost all patients were symptomatic at time of presentation (96.4%) with the main presenting symptoms of per vaginal bleeding in 91.1% and abdominal pain in 19.6% of patients. However, majority of the patients (55.4%) did not have any remarkable physical finding when they presented. For the rest of them, the commonest physical finding was the presence of abdominal mass (39.3%). Ultrasound was the main imaging modality. The main sonographic features of patients with endometrial carcinoma were abnormal thickened endometrium equal or greater than 5 mm (85.7%) which were common in the postmenopausal patients (46.4%) and enlarged uterus (48.2%). The preferred first line of diagnostic test was pipelle sampling (42.9%), followed by hysteroscopic tissue biopsy (28.6%). When the disease was staged, majority of patient were in stage I (67.9%). For other stages, 8.9% of patients were in stage II, 19.7% were in stage III and 3.6% in stage IV. The commonest histological type was the endometrioid adenocarcinoma with its subtypes (87.5%). The other types of histology were less common, with serous cell type in 3.6% of cases, clear cell type in 3.6%, mixed adenocarcinoma in 3.6% of cases and undifferentiated type in 1.8%. With regards to histological grades, many tumours were grade 1 (41.1%) and grade 2 (39.3%) and only 19.6% were grade 3 tumours. The predominant histological type of tumours with grade 1 and grade 2 were endometrioid adenocarcinoma, whereas for the grade 3 tumours were usually the other carcinoma subtype (serous cell, clear cell, mixed adenocarcinoma, and undifferentiated). The

endometrioid adenocarcinoma types of tumours were commonly occurred in early stages and in patient at age below 60. From the aspect of treatment, all patients had undergone surgery through the course of treatment. For modalities of treatments, majority had surgery followed with adjuvant radiotherapy (46.4%), while other 39.3% of patients had undergone surgery only. For the types of surgery, the type of surgery performed on most number of patients was extrafacial hysterectomy and bilateral salphingo-oopherectomy (BSO) (46.4%), followed by simple hysterectomy and BSO (41.1%). Despite appropriate treatment, a small number of the patients still developed recurrence, and later death. 75.0% of patients were disease free after 24 months, while the rest of 25.0% developed recurrence within less than 24 months, with the most of the patients (12.5%) developed persistence disease within less than 6 months following treatment. 80.4% of patients were still alive after 24 months following treatment, while other 19.6% of patients died in less than 24 months, with the most death (12.5%) occurred in less than 6 months. The significant prognostic factor were stage (stage III, $p = 0.003$, adjusted HR 26.243) and histological tumour grade ($p = 0.015$, adjusted HR 10.887). The 2-years survival rate was 97.4% for stage I, 60.0% for stage II, 36.4% for stage III, and 50.0% for stage IV.

Conclusions:

Despite the inability to come up with survival rate of 5 years due to limitation of the study, the survival rates at 2 years had managed to show the strong prognostic influence of stage and grade.

INTRODUCTION

1. INTRODUCTION

1.1 The State of Kelantan

Kelantan is one of the 14 states of Malaysia, which is situated in the northeast part of Peninsular of Malaysia facing the South China Sea. It has a total area of 14,922 square kilometers. The state shares its borders with Pahang, Perak, Terengganu and on the north the Thailand. Based on the latest population census, Kelantan has a population of 1.6 millions. Kelantan state is divided into 10 administrative district or 'Jajahan'; namely Kota Bharu, Bachok, Pasir Mas, Tumpat, Pasir Puteh, Tanah Merah, Machang, Kuala Krai, Jeli and Gua Musang .The capital and royal seat of Kelantan is Kota Bharu.

95% of Kelantan's population are Malays, and Islam is the most influential religion in the state. Kelantan is an agrarian state with lush paddy fields, rustic fishing villages and beautiful beaches. It is also well known for its cottage industries (Batik and Songket), its exotic delicacies, shopping haven and its distinctive unique Malay cultures. Meanwhile the other industries is also emerging.

In 2006 the per capita income was RM 7985. In terms of public hospital facilities, there are 4 public hospitals with specialists in Kelantan, namely Hospital Raja Perempuan Zainab II (HRPZ II) in Kota Bharu, Hospital Universiti Sains Malaysia (HUSM), Hospital Kuala Krai and Hospital Tanah Merah.

1.2 The Hospital Universiti Sains Malaysia (HUSM)

The hospital was built in 1979 and started its operation in 1983. It is situated in Kubang Kerian which is 6.6 km from Kota Bharu. Initially, the hospital was built in 1977 under the Ministry of Health, but was acquired by Universiti Sains Malaysia to serve as teaching hospitals with financial costs of RM 29.5 million, along with the construction of the new Health Campus of Universiti Sains Malaysia. Since its conception, the hospital has been functioning to provide a training ground for its undergraduate and postgraduate student to learn valuable, hands-on clinical experience, and to provide the best health service in the east coast region.

Over the time, the hospital had evolved into among one of the prestigious and modern hospital in the east coast region. The hospital now are providing the best multidiciplinary and sub-speciality health service in the east coast region, with the capacity of 950 beds, complete with the latest advance medical equipments. It is also functions as the postgraduate training hospital.

In terms of its health service responsibility, the hospital mainly covers the districts of Bachok, Pasir Puteh and the bordering district of Besut, Terengganu, and at the same time accepts patients from other areas as well.

1.3 The Obstetrics and Gynaecology Department, HUSM

The department started its operation alongside with the hospital. Currently, the department of Obstetric and Gynaecology (O&G) is staffed by 11 consultanst/ specialists, 8 registrars and 20 postgraduate medical officers. The post graduate programme began in 1991 and had produced the first batch of Master of Medicine in Obstetric and Gynaecology in 1995. It is now considered as one of the top, prestigious postgraduate training centre for those

aspiring to pursue the higher career in obstetrics & gynaecology in Malaysia. The management unit is divided into four teams; team A, B, C, and D, with each team differentiated on subspeciality interest. Team A subspecialises in gynae-oncology, Team B subspecialises in urogynaecology and adolescent gynaecology. Team C subspecialises in subfertility, while Team D subspecialises in fetomaternal medicine.

The department facilities consists of one labour room, two antenatal wards, one postnatal ward and one gynaecology ward for in-patient services which are well staffed and equipped. For obstetrics operative service, there is one maternity operation theater which located inside the labour room. For gynaecological surgery, the cases are operated in the general operation theater, complete with intensive care unit (ICU) backup.

The O&G clinic provides the outpatient services for the obstetrics and gynaecology cases in general. There are also subspecialty clinic services namely the combined antenatal clinic, twin clinic, postnatal clinic, menopause clinic, molar clinic, infertility clinic, and urogynaecological clinic.

The department also functions as one of the premier gynae-oncology centre in the east coast region. At present, the gynae-oncology unit is managed by two gynae-oncologist, in collaboration with the Nuclear Medicine, Oncology and Radiotherapy Department. Routinely, the operation day for gynae-oncological cases usually takes places on every Monday and Wednesday in the general operation theater. These cases will be later seen in the general gynaecology clinic on Sundays and Tuesdays. For complicated gynae-oncological cases, they are reviewed together with the Oncology colleagues in the combined oncology clinic in the Nuclear Medicine, Oncology and Radiotherapy Department on every Monday, every second week of the month.

1.4 The Nuclear Medicine, Oncology and Radiotherapy Department, HUSM.

The department was established since 1995 to provide cancer treatment and nuclear medicine services to the east coast of peninsular Malaysia. It provides the state-of-art cancer treatment and nuclear medicine service to the community, with two oncologist under its wings. The services includes radiosurgery, intensity modulated radiotherapy, 3D conformal brachytherapy, intra/perioperative radiotherapy, high dose radio-iodine therapy and dose intense chemotherapy.

The faculties are involved with teaching and research in the field of cancer, medical physics and cancer nursing. The aim is to provide multidisciplinary cancer care and strive for improvement through addition of technology, teaching, collaboration, research and innovation.

1.5 Introduction to the study

Endometrial carcinoma is the most common gynaecological malignancy in the developed nations. Among all of female cancers, 4% comprises of endometrial cancer worldwide. In 2008, it is the sixth of most frequent cancer that affect the women worldwide, with estimated new cases of 287100 were diagnosed in 2008 (Jemal A. et al 2011).

In Malaysia, endometrial cancer is the sixth most frequent cancer that affects the Malaysia women, with 414 new cases reported in 2007 alone, which is 4.0% from the total number of female cancers. The crude incidence rate (CR) was 3.3 per 100,000 women, with age standardised rate (ASR) of 3.9 per 100,000 women. The incidence occurs commonly among the Malays, with 47.1% of cases, followed by Chinese in 38.6% of cases, then Indians in 8.2% of cases (O Zainal Ariffin et al 2011).

The lifetime risk of developing endometrial cancer is estimated to be as high as 2.6%. The peak incidence of endometrial cancer is in the early sixth decade. However, endometrial cancer is being diagnosed increasingly in younger women. 1.6% of all endometrial cancers were diagnosed between the ages of 20 and 34 years and 6.1% between the ages of 35 and 44 years. Most of these are Type 1 or hormone-dependent cancers associated with endometrial hyperplasia. In most women, endometrial cancers are diagnosed at early stage and is usually associated with a good prognosis. With appropriate treatment, the 5-year survival for disease confined to the uterus is as high as 96%. (Arora et al 2012).

As the current trend of this disease continues to persist, this study tries to look into the trend of endometrial carcinoma cases that had been managed in HUSM from January 2002 until December 2011.

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 Types of endometrial cancer

Endometrial carcinoma is classified into two types based on clinical and molecular characteristics according to Bokhman (Bokhman 1983). Type I endometrial cancers are oestrogen dependent, which related to exposure to unopposed endogenous or exogenous oestrogen. The cancer usually arises on a background of atypical endometrial hyperplasia, and has association with nulliparity, obesity, hyperoestrogenism and insulin resistance. It is commonly occurs in pre or postmenopausal women. About 80% of endometrial cancer are Type I, which the predominant histological type is endometrioid adenocarcinoma, accounting for 75 to 80% of endometrial cancer. This tumour is usually low grade, with minimal myometrial invasion. This type of endometrial cancer also behaves less aggressive, and has better prognosis.

In contrast, the Type II cancers are not related to oestrogen, with the background of atrophic endometrium. The incidence is high among the postmenopausal age, thin and multiparous women. The main histological types of tumours are papillary serous cell and clear cell carcinoma. This tumour tends to be in higher grade, with deep myometrial invasion. It also behaves more aggressive with poorer prognosis (Bokhman 1983).

At molecular level, the progesterone receptor and oestrogen has higher positivity in grade 1 tumour in Type I endometrial cancer, in contrast to Type II endometrial cancer in which those receptors were negative. At genetic level, in Type I endometrial cancer the phosphatase and tensin homolog (PTEN) mutation and tumour protein p53 (p53) over expressions are rare, where as in the Type II endometrial cancer the over expression of p53 is found positive in 75-100% of tumours (Kurman et al 1994).

The histological types of endometrial carcinoma are classified according to the World Health Organization (WHO) classification (Silverberg et al 2004) (Appendix A).

2.2 Risk factors

In general, the Type I endometrial cancer is due to prolonged exposure to oestrogen, either from endogenous or exogenous oestrogen. In that case, patients with condition that leads to hyperoestrogenism, such as obesity, polycystic ovarian syndrome, late menopause, and oestrogen producing tumour are at risk. The risk is more for postmenopausal obese women due to the effect of unopposed oestrogen from the peripheral fat conversion. In premenopausal women, obesity causes insulin resistance, ovarian androgen excess, anovulation and chronic unopposed oestrogen. Diabetes and hypertension are the recognised risks independent of their association with obesity (Brinton et al 2014).

Some drugs are also known to be associated with endometrial cancer. The use of unopposed exogenous oestrogen increases the risk of endometrial cancer to 9.5 times. The use of Tamoxifen which is usually used as adjuvant treatment of breast cancer, increase the risk by 7.5 times after 5-year of usage. The risk remains even after stopping the drug (Assikis et al 1995). The use of combined oral contraceptive pills for 1 year decreases the risk by more than 40%, and women on combined hormonal replacement therapy also have lower risk if the progestogen content is more than 10-12 days per cycle (Garrett et al 2008).

Endometrial hyperplasia is often thought as the precursor to the development of Type I endometrial cancer. This is due to the fact that hyperplasia is the results of excessive or unopposed oestrogen stimulation of the endometrial glands, or abnormal endometrial response toward normal hormonal stimulation. If left untreated, it can progress to adenocarcinoma. The risk of simple hyperplasia, complex hyperplasia, and atypical

hyperplasia to change into adenocarcinoma is 1%, 2.4%, and 46.2% respectively (Horn et al 2007).

2.3 Presentation and Diagnosis

The main presenting complaint for endometrial cancer is abnormal per vaginal bleeding, mainly as postmenopausal bleeding. It occurs in about 80% of patients with endometrial cancer. Other symptoms are abnormal per vaginal discharge, and symptoms due to enlargement of uterus, such as lower abdominal pain and compressive symptoms, and other symptoms indicative of extrauterine spread. The common signs are enlarged uterus, cervical and vaginal mass which indicate the spread of the disease.

Full evaluation of the endometrium by ultrasound and endometrial biopsy should be performed in patients with postmenopausal bleeding. With the cut-off point of 5 mm and more, ultrasound was shown to have 80.5% sensitive and 85.7% specific in detecting endometrial cancer (Jacobs et al 2011).

On the other hand, thin (< 5 mm) endometrial measurement on transvaginal ultrasound excludes endometrial disease in the majority of postmenopausal women with vaginal bleeding, regardless of the hormone replacement usage (Smith-Bindman et al 1998). Pipelle sampling, in combination with thick endometrium increases the sensitivity to 87.5% with a specificity of 87.8% (De Silva et al 2007). Therefore, in most patients the pipelle sampling is as good as endometrial curettage. Hysteroscopy is indicated if the pipelle results was inconclusive, insufficient, or having persistent symptoms despite of normal endometrial biopsy (Litta et al 2005).

In regards to tumour marker, there is no established tumour marker in endometrial cancer. The cancer antigen 125 (CA 125) level is mainly elevated in 65-80% cases of advance stage disease, where the tumour has spread to ovaries or peritoneum. The magnetic resonance imaging (MRI) is used to evaluate the myometrial invasion, whereas the computed tomography scan (CT scan) is better in assessing the retroperitoneal lymph nodes (Epstein et al 2014).

2.4 Staging

Endometrial cancer is staged through surgico-pathological staging. The stage is divided in Stage I, II, III and IV. The latest standard stage classification is the International Federation of Gynaecology and Obstetrics (FIGO) corpus uteri cancer staging 2009 (Appendix B) (Amant et al 2012). The previous stage was the 1988 FIGO corpus cancer staging. There are a few changes from the old staging; the no myometrial invasion and less < 50% invasion are now combined, as there was little survival difference between these two. The cervical involvement of gland and stroma is also now combined for the same reason. The parametrial involvement is now included. The peritoneal fluid for cytology has been eliminated as it was found that the result based on sampling of washing is highly variable. The pelvic and para-aortic lymph nodes metastases carry different survival and have to be separated in the staging (Amant et al 2012). In addition to that, the histological grade is also included along the surgical staging in the 2009 FIGO staging system. The methods of grading are by architectural growth pattern (adenocarcinoma component); Grade 1: ≤ 5% tumour is in solid sheet, Grade 2: 6-50% of tumour is in solid sheets and Grade 3: > 50% tumour are in solid masses. Notable nuclear atypia (grade 3, nuclear features) will raised 1 grade. The second method of grading is by nuclear features (for non-serous carcinoma); Grade 1: round

to oval with even distribution of chromatin and inconspicuous nucleoli, Grade 2: irregular, oval nuclei with chromatic clumping and moderate size nucleoli, and Grade 3: large pleomorphic nuclei with coarse chromatin and large, irregular nucleoli (Amant et al 2012).

2.5 Treatment

The mainstay of treatment for stage I endometrial cancer is surgery, in which the preferred type is extrafacial total abdominal hysterectomy and bilateral salpingo-oophorectomy, with pelvic and para-aortic lymphadenectomy in selected cases. Two large independent surgical randomized controlled trials found that routine pelvic and/or para-aortic lymphadenectomy confer no therapeutic benefit (Kitchener et al 2009). A pelvic lymphadenectomy is performed in patients with a preoperative biopsy showing grade 2–3 endometrial cancer and myometrial invasion greater than 50% on MRI (presumed stage IC, grade 2–3). Para-aortic lymphadenectomy is reserved for clinically enlarged lymph nodes at MRI or laparotomy.

The role of radiotherapy is mainly as the adjuvant therapy following surgery in early-stage disease. It also provides good palliation for advanced-stage disease. In patients with early stage I in any grade, which had been treated with surgery plus adjuvant radiotherapy, only 4.2% had develop recurrence as compared with 13.7% of patients who were treated with surgery only (Creutzberg et al 2000). For stage II, the 5-year overall survival rate was 84% and the disease-free survival rate was 97% (Fanning et al 2001).

The role of chemotherapy is less well established. It might be benefited for the high risk, advance cases.

The hormonal therapy is used on patient with extreme comorbidities, young patient who wants to reserve the fertility function, and where surgery or radiotherapy cannot be used (Thigpen et al 1999).

2.6 Prognosis

The outcome following appropriate treatment is usually good in the early stage, but poor in advance stage. The 5-years survival rate for stage I is 81-91%, stage II is 71-79%, stage III is 50-60% and stage IV is 5-15% (Creasman et al 2003). Recurrence usually occurs within the first 2 years after treatment, and tends to recur in the pelvis where it frequently occurs at the vaginal vault.

RATIONALE OF THE STUDY

3. RATIONALE OF THE STUDY

It is important that a gynaecological cancer database or registry which includes endometrial cancer is formed and regularly updated. Until this point there is still no standard database available in this centre. Therefore this study will provide us with its own statistical data, which can be analysed. The results can be used to improve our quality of care and the cost effectiveness of treatment. It is also can be used as the groundwork for the future research. With the availability of our own data, it also can lead to better counselling of the patients.

STUDY OBJECTIVES

4. STUDY OBJECTIVE

4.1 General objective:

To perform a retrospective review on endometrial carcinoma cases treated at the HUSM over a 10-year period, between January 2002 and December 2011.

4.2 Specific Objectives:

1. To determine the prevalence of endometrial carcinoma in HUSM.
2. To evaluate the response of all treatment modalities in the treatment of endometrial carcinoma patients.
3. To determine the incidence of recurrence of ovarian cancer treated in HUSM.
4. To study the survival rate of endometrial carcinoma cases following the standard treatment.

METHODOLOGY

5. METHODOLOGY

5.1 Study Design:

This study was a retrospective record review, covering the ten year period from 1st January 2002 until 31st December 2011.

5.2 Study setting:

The study was conducted in HUSM, Kubang Kerian, Kelantan.

5.3 Reference Population:

All the endometrial carcinoma cases diagnosed and managed at HUSM during the period mentioned above.

5.4 Source Population:

All patients who diagnosed as endometrial cancer and had further followed up at HUSM for at least 2 years period of time.

5.5 Sample Size Determination:

The sample size was calculated using power and sample size calculation, PS software version 3.0 (2009).

Significant level = 0.05

Power = 0.8

Hazard ratio = 2

Median hazard time; m1 = 60, m2 = 12 (Creasman et al 2003)

Accrual time = 60

Additional follow up = 12

Calculated number of cases = 18

30% loss to follow up was added to the final figure.

Therefore, the calculated number of case was at least 24.

5.6 Inclusion Criteria:

1. All patients with diagnosis of primary endometrial carcinoma at HUSM from January 2002 – December 2011.
2. Surgical staging following FIGO classification 1988 and 2009.
3. Had tissue diagnosis by histopathological examination (HPE).
4. Primarily managed by HUSM.

5. Duration of follow up at least 2 years of durations

5.7 Exclusion Criteria:

1. Patient with secondary endometrial carcinoma or with other concurrent cancer.

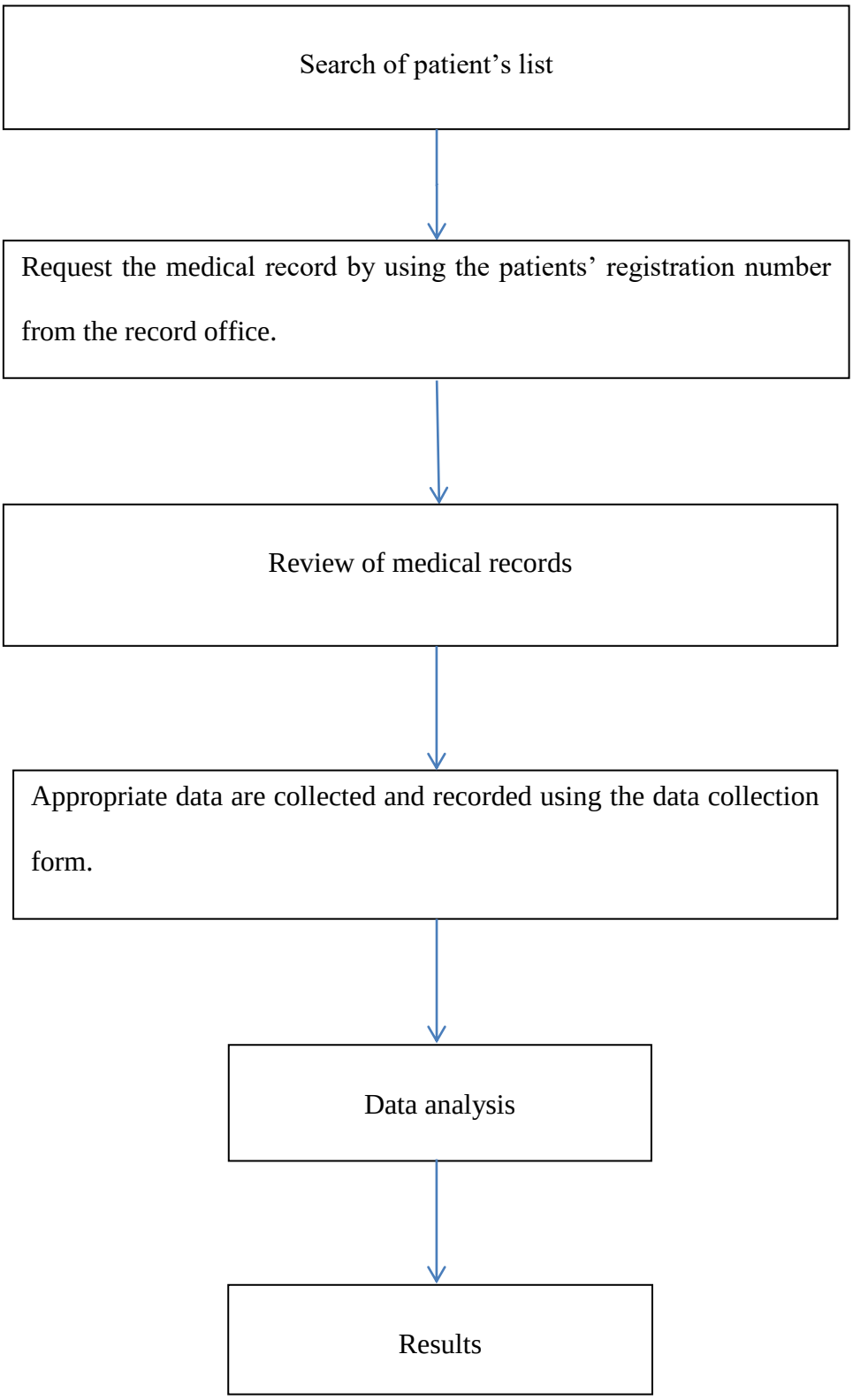
2. Inadequate information.

5.8 Flow of the study:

Firstly, the approval to conduct the study was obtained from the Department of Obstetrics & Gynaecology, and from the Research Ethical Committee, HUSM.
The permission to review the patients' medical record was granted by the Director of HUSM and was granted.

All information about the endometrial cancer cases was collected by reviewing the patient medical records traced from the HUSM Record Office, after obtaining the patient registration number from the central patients' registry via computer or manually. To narrow down the search the diagnosis keyword in accordance to International Classification of Diseases (ICD-9 and ICD-10) is used, which are "uterine cancer", "uterine carcinoma", "endometrial cancer", "corpus uteri cancer" and "uterine carcinoma". All relevant data was entered into the Data Collection form and analysed. For standardisation, the FIGO 2009 staging for cancer of corpus uteri was used. The statistical data analysis will be processed using the computer IBM® SPSS® Statistics version 20.0 software. The summary of the flow of the study is shown in the flow chart below:

Figure 1: Flow chart of the study



RESULTS

6. RESULTS

6.1 Overview of study population

A total of 72 cases were initially reviewed. From that numbers, 16 cases had to be excluded from taking part in the study due to incorrect diagnosis, many missing information and not fulfilling the inclusion criteria. A final number of 56 cases were finally included in this study.

Table 6.1: Age distribution among the endometrial carcinoma patients (n = 56)

Age group (years)	No. of cases (n)	Percent (%)
30 - 39	10	17.9
40 - 49	6	10.7
50 - 59	24	42.9
60 - 69	9	16.1
70 - 79	7	12.5
Total	56	100

Mean (SD)	t statistic (df)	p value*
54.3(11.77)	2.146 (55)	0.036

*One sample t test