A REVIEW OF CERVICAL CANCER IN HUSM FOR 15 YEARS PERIOD, FROM 1996 to 2010

BY

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Dissertation Submitted In Partial Fulfillment Of The
Requirement For The Degree Of
Master Of Medicine
(Obstetrics and Gynaecology)

UNIVERSITI SAINS MALAYSIA
2014

ACKNOWLEDGEMENT

Alhamdulilah. Praise to Allah S.W.T and His 'Rasul' for the completion of the study. My Deepest gratitude goes to those who have made this study accomplish.

I would like to express my thanks to Profesor Nik Mohd Zaki Nik Mahmood as my supervisor for both along the study and during my master program in Universiti Sains Malaysia for all the guidance and supervision. Many thanks to staff from record unit, obstetric and gynaecology department for their cooperation and support. Not to forget my fallow colleague in the master programe who had never fail to assist me in the process.

Special thanks to Dr Zahirudin and Dr Che Muzaini , lecturer of comunity medicine department who had assisted me in the statistical part that always puzzle me. Last but not least, my gratitude goes to my parent (Hj Nawi Othman and Hjh Noraina Abdullah), my dear wife (Dr Nurul Nurasikin) , and my dearest children (Nazmi and Marissa) for the encauragement, support, and the time that they had spare for me to complete the desertation

Mohamad Maulizal Bin Nawi @ Narawi

JUNE 2014

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ABBREVIATIONS AND GLOSSARY

Adj	Adjuvant
ASR	Age Standardized Incidence
CA	Carcinoma
CI	Confident Interval
CIN	Cervical Intraepithetial Neoplasm
CCRT	Concurrent chemoradiation
DNA	Deoxyribonucleic Acid
FIGO	International Federation Of Gynaecologocal Oncology
GIT	Gastrointestinal tract
HPV	Human Papilloma Virus
HUSM	Hospital Universiti Sains Malaysia
ICC	Invasive Cervical Carcinoma
IT	Information Technology
MOH	Ministry Of Health Malaysia
O&G	Obstetric and Gynaecology
PST	Pap Smear Test
RT	Radiotherapy
SCC	Squamus Cell Carcinoma
UK	United Kingdom
USA	United State Of America
USM	Universiti Sains Malaysia
UTI	Urinary tract infection

ABSTRAK

Tajuk:

 Kaji selidik berkaitan Kanser Pangkal Rahim di Hospital Universiti Sains Malaysia (HUSM) dalam tempoh 15 tahun bermula pada Tahun 1996 sehingga tahun 2010

Objektif:

Objektif umum kajian ini adalah bertujuan meneliti kes kanser pangkal rahim yang menerima rawatan di HUSM dari tahun 1996 sehingga tahun 2010. Bagi objektif specifik, kajian ini bertujuan mengenalpasti ciri-ciri berkaitan kes kanser pangkal rahim yang mendapatkan rawatan di HUSM. Ia juga bagi membandingkan epidemiologi kes kanser pangkal rahim untuk lima tahun kedua dan ketiga tempoh kajian. Kajian ini antara lain mengenalpasti dan membandingkan faktor faktor penting berkaitan kes peringkat awal dan kes   peringkat akhir kanser pangkal rahim dalam menentukan kematian atau perkara yang memburukkan lagi keadaan pesakit.

Metodologi:

Kajian retrospektif ini dijalankan dengan menganalisa semua rekod pesakit-pesakit kanser pangkal rahim yang telah menerima rawatan di HUSM dari tahun 1996 hingga 2010. Semua maklumat yang diperlukan didapati dari rekod pesakit dan direkodkan pada borang data yang diseragamkan.

Keputusan:

Sebanyak 221 kes kanser pangkal rahim yang telah terlibat dalam kajian ini. Majority adalah berbangsa Melayu. Walaupun demikian didapati berdasarkan peratusan penduduk di Malaysia dan Kelantan, masyarakat Cina didapati mempunyai risiko kanser pangkal rahim yang sedikit tinggi berbanding Melayu. Secara purata umur pesakit ialah 54 tahun. Dalam Julat berkumpulan kebanyakan pesakit berusia dalam lingkungan umur 50-59. Berbanding dengan negara maju seperti UK yang mempunyai 2 kali kenaikan kes kanser rahim berbanding julat usia. Peningkatan ketara yang di perhatikan adalah sekali sahaja, berdasarkan fakta terbabit, kenaikan terbabit kemungkinan besar berkaitan dengan faktor peningkatan risiko kanser dengan usia dan juga faktor sejarah alami penyakit kanser pangkal rahim yang mengambil masa 10-20 tahun dari jangkitan HPV yang awal.

Didapati bahawa case kanser pangkal rahim adalah berkait rapat dengan jumlah penduduk di kawasan yang terlibat, dimana Kota Bharu dan Kuala terengganu didapati mempunyai jumlah pesakit kanser pangkal rahim paling ramai di dalam negeri masing masing. Ini kerana, sebagai ibu negeri kepadatan penduduk adalah lebih tinggi. Purata usia pesakit dalam kajian ini ialah 54 tahun. Majoriti pesakit dalam lingkungan usia lima puluhan (dlm julat usia 50-59 tahun). Secara keseluruhan, pesakit kanser pangkal rahim yang terlibat dalam kajian ini merupakan pesakit yang asalnya sihat dan berupaya menguruskan diri sendiri semasa datang ke HUSM (84%). 95.5% pesakit pernah berkahwin dan secara purata mempunyai 5 anak. Lebih separuh pesakit telah putus haid (55.7%). Adalah didapati bahawa lebih 90% daripada pesakit dalam kajian ini tidak pernah melakukan ujian pap smear. Namun, kajian ini gagal mengaitkan tabiat merokok

(hanya 5%) dan sejarah keluarga yang mempunyai kanser (2.7%) dengan kanser pangkal rahim. Sementara itu, mendapatkan sejarah seksual merupakan perkara yang sukar dan selalunya kurang disenangi dalam populasi kajian ini. Oleh itu kemungkinan yang amat besar bahawa jumlah pesakit atau pasangan yang mempunyai berbilang pasangan seks adalah jauh lebih tinggi. Disamping itu,didapati bahawa usia purata pesakit mula aktif secara seksual pada usia 20 tahun. Kebanyakan pesakit di rujuk dari hospital pakar yang lain (54%). Sebilangan besar pesakit mengadu mengalami pendarahan selepas putus haid (38.9%) dan pendarahan selepas melakukan hubungan kelamin (38.5%).

Majoriti pesakit disahkan menghidap penyakit kanser pangkal rahim pada tahap 2B iaitu 31.2% dan 3B 25.3%. Seperti negara membangun dan mundur yang lain, pesakit dalam kajian ini sudah berada pada tahap akhir penyakit semasa datang untuk rawatan (67.4%). Hanya 32.6% masih pada tahap awal. 78% histologi adalah SCC dan 15.4% merupakan adenocarcinoma. Berdasarkan sumber skan CT yang terbatas 84.6% mengalami penyakit yang melibatkan sangkar pelvik sahaja. Sesuai dengan jumlah pesakit yang kebanyakan datang pada peringkat akhir, 61.5% pesakit diberikan radioterapi dan kemoterapi sebagai rawatan primari. Hanya 60 pesakit menjalani pembedahan. 80% daripadanya tidak mengalami sebarang komplikasi.

120 pesakit sembuh sepenuhnya dan secara purata kekal sihat sehingga 36 bulan. Bagaimanapun sehingga 65% pesakit telah ingkar rawatan dan temujanji susulan. Kebanyakan pesakit yng mempunyai penyakit berulang mengalami masalah itu pada julat masa selepas 12 ke 36 bulan, begitu juga dengan kes kematian.Sebanyak 49

pesakit mengalami penyakit yang berterusan walaupun setelah diberikan rawatan. 13% daripada kematian disebabkan bukan atas sebab-sebab kanser

Jika dibandingkan antara kes pada 2001 sehingga 2005, dan 2006 sehingga 20o6,terdapat beberapa data yang wajar diberi perhatian. Terdapat sedikit kenaikan dari segi jumlah pesakit dari Terengganu dari 20 ke 28%.Dalam masa yang sama terdapat pengurangan pesakit berbangsa cina dari 13 ke 6.6%. Risiko berkaitan adalah hampir sama dengan populasi secara keseluruhan. Didapati bahawa pesakit pada tahap 1b2 meningkat dari 6 ke 12%. Ini kemudiannya turut mempengaruhi jumlah pesakit yang dirawat dengan pembedahan diikuti radioterapi dan chemoterapi selepas pembedahan yng turut meningkat dari 10 ke 19%. Penyakit berulang yang awal (dalam tempoh 6 ke 12 bulan) hampir 3kali ganda iaitu 4.6 kepada 13.9. Sebab musabab adalah sukar ditentukan. Kadar kematian juga berlainan, dimana pada 2001-2005, hanya 53% kematian dalam 36minggu. Manakala pada 2006 ke 2010 jumlahnya meningkat kepada 72%.

Berkaitan dengan perbandingan pesakit di tahap awal dan akhir pula. Didapati pesakit di tahap awal adalah lebih muda, dimana majoriti pada usia empat puluhan, manakala pesakit pada tahap akhir pula di usia lima puluhan. Pesakit dari Terengganu 3 kali lebih risiko untuk menghidapi penyakit kansr pangkal rahim pada tahap akhir berbanding Kelantan. Begitu juga dengan pesakit yang dirujuk oleh doktor dari pusat rawatan tertiari. Pesakit yang telah putus haid 2.5 kali lebih berisiko untuk datang dengan penyakit pada tahap akhir sehingga 2.5 kali. Pesakit pada tahap akhir berkebarangkalian lebih tinggi untuk ingkar rawatan susulan dan temujanji pada tahun pertama iaitu 41% berbanding 225 pada tahap awal. Kebanyakan kematian dalam kalangan pesakit tahap akhir berlaku dalam 6 bulan pertama.Manakala untuk tahap awal kebanyakan kematian berlaku dlm tempoh 12 ke 36 bulan.

Kesimpulan:

Walaupun tidak berjaya mengenalpasti jangka hayat pesakit dengan tepat kerana masalah logistik , kajian ini telah menunjukkan dengan jelas ciri ciri kes kanser pangkal rahim yang terlibat dalam kajian ini. Faktor utama yang mempengaruhi prognosis pesakit merupakan tahap penyakit itu. Adalah dibuktikan bahawa perubahan positive tidak berlaku dalam masa yang singkat. Walhal untuk kes kanser pangkal rahim, meningkatkan jumlah orang ramai yang menjalani ujiaan pap smear dan menjalankan pap smear pada usia sasaran yang betul dan seterusnya merawat pesakit terbabit adalah kunci untuk meningkatkan hasil secara keseluruhan.

ABSTRACT

Topic:

A Review of Cervical Cancer in HUSM for a 15 years period from 1996 to 2010

Objective:

This study was designed to review the cervical cancer cases that presented to HUSM between 1996 to 2010. In specific, it involved determination of characteristic of cervical cancer cases in HUSM during this period. This study also compared the epidemiology trend of cervical cancer in HUSM in the second and third 5 years period of the study. Apart from that, it also determined and compared the associated factors between early versus advanced cervical cancer in relation to morbidity and mortality in HUSM during the period

Methodology:

This retrospective study was conducted in HUSM for a period between 1996 to 2010. It covered all the 221 recorded case of cervical cancer that been admitted and primarily treated in HUSM . All their medical records were review and related information were entered in a standard data collection form.

Results:

There were 221 cervical cancers cases involved in this study. The vast majority were Malay ethnic. Base on Malaysian and Kelantan population study, it can be concluded that Chinese ethnic group had slightly higher risk to developed cervical cancer. 72% of patients were from Kelantan and 25% from Terengganu. Most came from the capital

city of Kelantan and Terengganu due to its high population. The mean age of the patients diagnosed to have cervical cancer in this study was 54 years old. The majority of the patients were in the 50th decade of their life (age 50-59 years old). Generally patients that presented in this study were healthy patients with no comorbid (84%). All of the patients were married. Vast majority (95.5%) were multiparity with average parity of 5. More than half patients were postmenopausal (55.7%). There were very high correlation between not doing any pap smear to cervical cancer as 90% of patient never did any pap smear before. However poor corelation between smoking (5%) and family history of malignancy(2.7%) to cervical cancer in this study. Obtaining sexual history were not an easy task in this population. It was considered as humilation and for some as dysrespect. Thus it was very highly likely that the number of patients or partners with multiple sexual partners will be far less then it really were. Meanwhile, mean age of sexual exposure was 20 years old. Most patients were referred to HUSM by terteiry centre for further treatment 54%. Most patients either presented with PMB (38.9%) or PCB (38.5%).

Majority of patients presented during stage 2B (31.2%) and 3B (25.3%). As per other underdeveloped country, 67.4% of cases were in their late stage. Only 32.6% came when the diseases still early. 78% were SCC, 15.4% were adenocarcinoma. Base on limited CT scan report 84.6% were locally advance disease. Correspond to stage at presentation 61.5% were treated with Rtx/ CCRT. Only 60 patients undergo surgical intervention with 80% without any complication. Of that, 77% had no dyscrepancy between clinical and surgical staging.

120 patients were disease free. The average were 36 months. However up to 65% defaulted their follow up and never turn up thereafter. Most patients that had recurrent presented in >12 to 36month periods, so did the death. However 49 patients having progressive disease. Up to 13% of patient that died due to non cervical cancer causes

The comparison between year 2001-2005 and 2006-2010 shows few promising data. There were slight increased patients from terengganu (20 vs 28%) and coincidental reduce in chinese patient from 13 to 6.6%. The risk factor were comparable to general population of the study. In term of stages, the prominant changes were double the case of 1b2 disease (from 6 to 12%). This were likely influenced the increased surgery and adjuvant Rtx/CCRT in 2006-2010 periods. Early recurrent (within 6-12 months periods) were almost triple (from 4.6 to 13.9%). The exact cause were unknown. The death were also different,where by in the earlier year had only 53% death within 36 months,while in later years the percentage of death at the same periods were 72%.

Regarding the factor between early and late disease. It was noted that patients with early stage were majority in 40th decades, whereby the late stage group were majority in 50th decades. Patients from Terengganu had 3 times likely late stage compare those from Kelantan. So did patients that referred by terteiry centre (with Odd 2.5) Postmenopausal were more associates with late disease with odd more than 2.5 times. The late stage groups had higher defaulter percentage in the first year of diagnosis (41% compare to 22% in early stage). There were significantly more death at late stage arm. The majority death in late stage were within 6 months (46%), while in early stage were in >12 to 36months periods (29.6%).

Conclusion:

Despite the innability to come with survival rate secondary to logistic problem, the study had shown the character of cervical cancer in HUSM. The main prognosis were still the stage of the disease. It was also proven that positive changes were not achieved easily with time alone. Thus wide coverage of screening with right targetted population to detect precancerous lesion and early disease, follow by proper treatment is the key to successfull in overall outcome of cervical cancer.

INTRODUCTION

INTRODUCTION

1.1)   The State of Kelantan

Kelantan is situated in the northeast part of peninsular malaysia facing the South China Sea.It has a total area of 14,922 square kilometers. The state share its borders with Pahang, Perak, Terengganu and on the north the Thailand.Base on the latest population census, kelantan has a population of 1.6million. Kelantan state is devided 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 ethnic Malay, and under the Malaysian Constitution, all Malays are Muslims; therefore, Islam is the most influential religion in the state. Kelantan is an agrarian state with lush paddy fields, rustic fishing villages and casuarina-lined beaches. It also well known for it cottage industries (Batik and Songket).Meanwhile the other industries is also emerging.

In 2006 the perkapita income was RM7985. There are 4 goverment hospital with specialist in Kelantan, namely Hospital Raja Perempuan Zainab II (HRPZ II), HUSM, Hospital Kuala Krai and Hospital Tanah Merah.

1.2)   The Hospital Universiti Sains Malaysia (HUSM)

The hospital is built in 1979 and started its operation in 1983. It is built as part of the Health Centre Of Universiti Sains Malaysia. It is situated in Kubang Kerian which is 6.6 km from Kota Bharu. HUSM Teaching and Referal Hospital is an excellent quality service and the latest technology. The hospital is committed to provide the best for each patient by applying the values of quality in the performance of charter hospital. The hospita aim is to satisfy customers in order to achieve well-being entrusted by the government. The Hospital also committed to provide adequate facilities to ensure that graduates are skilled and competent.

As an outstanding corporate organization, Hospital Universiti Sains Malaysia provide patient care services that operate based on:

- Efficiency in the administration and management
- Quality in services
- Interested in teaching and research activities
- Generation of optimal financial
- Construction of human values
- Preservation of social responsibility towards society

Patient that came to HUSM came from all part of Kelantan. Hovewer the hospital cover mainly nearby area, Bachok, Pasir Puteh and north Terengganu(Besut).

1.3) The Obstetrics and Gynaecology Department, HUSM

The department start it operation alongside with the hospital. In 2010 the department of Obstetric and Gynaecology (O&G) was staffed by 11 consultant/ specialist, 10 registras and 22 medical officers. The post graduate programme was started in 1991 and the first batch of Master of Medicine in Obstetric and Gynaecology was graduated in 1995.The O&G clinic is situated on the ground level. All of the clinics are conducted on daily basis. The labour ward and departmental office was located at the first floor, above the clinics. The antenatal and postnatal ward is located at the 3rd floor.Whereby the gynaecology ward is located at the level one of the main building of the hospital.

The management unit was devided into four teams, A,B,C,D. Each teams are each sub speciality oriented. Team A, subspecializes in Gynaeoncology,Team B subspecialized in urogynaecology and adolescent gynaecology. Team C specialized in Subfertility. While Team D subspecialized in Fetomaternal medicine.

1.4) The Nuclear Medcine, 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 provide state-of-art cancer treatment and nuclear medicine service to the community. The services includes radiosurgery, intensity modulated radiotherapy, 3D conformal brachytherapy, intra/perioperative radiotherapy, high dose radio-iodine therapy and dose intense chemotherapy.

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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

Cervical Cancer is the fourth most common cancer in female worldwide. It has been estimated that up to 528,000 new case reported annually and responsible for almost 266,000 deaths annually, however the incident of the disease is not equal worldwide of which about 85% occurred in developing countries or economically disadvantage area. Incidence and mortality rates of Invasive Cervical Cancer (ICC) have fallen over the past decades in a number of countries, mainly in high-resource countries following the introduction of screening programmes for cervical cancer. However, stable or even rising trends have been observed in countries where screening activity is either lacking or suffers from low-quality and low-coverage. Region with high risk of ICC are Eastern Africa (ASR 42.7 per 100,000 population), Western Africa (ASR 33.3). While the lowest incidence is observed in Australia and New Zealand (ASR 5.5) and western Asia ASR 4.4 per 100,000 population.

 In South East Asia,The ASR is 15.8 per 100,000 population with great difference base on the particular area.

In Malaysia, according to the Third Report of the National Cancer Registry in 2006, the incidence of cervical cancer is 12.2 per 100,000 populations. In 2006 ,1074 new cases were reported. About 3,000 cases were treated in public hospitals. The incidence was

highest between the ages of 50 and 69. About 50% of the cases were diagnosed between the ages of 35 and 55. Chinese women had the highest ASR of 23.2 per 100,000 populations, followed by Indians with ASR of 16.4 per 100,000 populations and Malays with ASR of 8.7 per 100,000 populations . Compared to Chinese women in other Asian countries, the incidence of cervical cancer in the Malaysian's Chinese is among the highest.

In Kelantan itself, the annual incidence of cancer of the cervix every year for this state is approximately 11% per 100,000. In 2006, only 38,171 number of pap smear done from various service provider.

The major risk factor, indeed the necessary event for developing Pre invasive and CA of cervic is human papilloma virus (HPV) infection. This had been proof via scientific evidence obtained from clinical, epidemological, virological, molecular data that demonstrate conclusively that ICC is due to persistant infection by a huigh risk HPV. HPV is a DNA virus which does not have an envelope but it consists of shell called capsid. HPV DNA is circular and double-stranded. HPV DNA or genome has three major regions i.e Long Control region, E region and L region. Based on the sequence of genes in the E6, 7and L1 regions, thereare more than 200 HPV subtype and at least 13 of them are categorized as high risk HPV type because of their oncogenic properties. HPV has been attributed to many skin andmucosal diseases ranging from benign viral warts to a malignant disease such as cervical cancer, vulvar cancer, vaginal cancer, penile cancer, anal cancer and also a neck cancer.

HPV 16 and 18 have been attributed to at least 65-75% of invasive cervical cancer in Asia,and South /central America (Smith Js 2007). Other High Risk HPV is 31, 33,35,45,52 and 58. High risk HPV is also responsible in preinvasive cervical lesions while low risk HPV especially Type 6 and 11 are responsible in at least 90% of anogenital warts. In invasive cervical cancer, high risk HPV has been attributed in 99.7% of cases.

HPV infection spread via direct contact. In case of ICC the transmission is almost exclusively through sexual contact. Low risk HPV can be transmitted vertically from the mother to the baby leading to respiratory papillomatosis. HPV infection is very common,esspecially in young women, however 70% of new infection resolved spontaneously within 1 year and almost 90% resolve in 2 years.

Other factor that widely recognized to be associate with cervical cancer is High parity, multiple sexual partner, early sexual exposure, chronic illness causing reduce immune system, low socio-economic status sexual transmitted disease, positive smoking history.

The natural history of cervical cancer and its etiology is well studied and understood. Early detection of pre invasive disease is the key prevention of CA cervix. Pap smear has been shown to reduce the incidence of invasive cervical cancer by as much as 80 percents (Lara E Et al 2009). Pap smear screening frequency of 3 yearly is able to reduce the cumulative risk of woman from invasive cervical cancer by 91 percents (BMJ sept 1986). Malaysian's Ministry of Health had allocated 3.55 millions Malaysian Ringgit in 2003 for the Pap smear screening program. Women who obtain Pap smear test from Public Hospital or other public health services do not need to pay for the

services. Majority of the pap smear test is conventional Pap smear and only a few Public Health Services and Private sectors are offering liquid based cytology.

In Malaysia, Pap smear screening program commenced in the late sixties and until the year 2000, only about 850,000 women have undergone Pap smear tests out of the eligible 5.2 million female populations (20 to 65 years).Until today, Pap smear screening program in Malaysia is based on opportunistic screening. Nevertheless, based on the 2nd National Health & Morbidity Study Report, only 26% of women in Malaysia had undergone the pap smear screening.

Malaysian National Cervical Cancer Guidelines 2003 and Guidebook in Pap smear 2008 recommended that all sexually active women age between 20 to 65 years should undergo Pap smear screening annually for two consecutive years and if the Pap smear is normal on both occasions, they can continue the screening test once every three years

Patient mostly asymptomatic in early stage of the disease. Patient might just presented with abnormal pap smear which later reveal an early stage of cervical cancer. Some patient might presented with asymptomatic cervical growth during pap smear screening.The most common presenting symptom is post coital bleeding. Some patient had Irregular per vaginal Bleeding and or postmenopausal bleeding. When the tumor get infected patient will have purulent PV discharge, fever and pelvic pain, which may associate with pyometra and heamatometra.

In advance stage, patient might presented with passing bloody stain mucus PV, pelvic pain, urinary symptom and constitutional symptom. Tumour in the pelvic may cause

compression and causing symptom of acute renal failure and deep vein thrombosis. While involvement of deep lymphatic system will cause lymphedema. Tenasmus and per rectal bleeding may direct to posterior tumour invasion.

Patient with distant metastasis may presented with shortness of breath, bone pain, severe headache, and neurology problem. In develop country up to 80% patient presented with stage 1 & 2 diseases. However in underdeveloped country, only 30 to 40% patient presented with early disease.

Cervical cancer patient should be ideally managed in an expertise centre to ensure patients get the optimum treatment. Treatment currently is base on stages of the cancer. However the final decision of the best treatment should be base on pathology information, extend of disease, patient age, fertility wishes, co morbidity, performance status and personal wishes.The principle of treatment is to decide the intention of treatment (curative or palliative) follow by offering the best treatment modalities. Treatment available can be classify into four. Surgery, Radiotherapy or chemoradiation, Chemotherapy or Combination therapy

Clinical stage is the most important prognostic factor. Overall 5 years survival rate for stage 1A ranging from ranging from 95 to 100%, for stage 1B ranging from 75 to 90%,and stage 4 had survival rate of 5%. Other factor effecting prognosis is depth of tumour invasion, lymphovascular space invasion and tumour volume or diameter . Patient with aggressive histology malignancy had poorer prognosis such as adenosquamous, small cell neuroendocrin, sarcoma and poorly differentiated tumour.

Other prognostic factor include age, general medical condition include co morbidity and nutritional status.

LITERATURE REVIEW

2) LITERATURE REVIEW

Introduction

Cervical Cancer is the fourth most common cancer for the women worldwide. It is the number seven in overall cancer worldwide. It account for 12% of total women cancer worlwide in 2012. Approximately 528,000 new cases of ICC leading to 266,000 death worldwide in 2012. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions. Mortality varies 18-fold between the different regions of the world. Region with high risk cervical cancer with the ASR more than 30 per 100,000 population are Eastern Africa (ASR 42.7. per 100,000 population), Melanesia (ASR 33.3), South Africa (ASR 31.5), Middle Africa (ASR 30.6). Region with lowest ASR were Australia / New Zealand (5.5) and Western Asia (4.4). For South East Asia the ASR were 15.8 per 100,000 population. (GLOBOCAN 2012)

In Malaysia, overall cancer ASR was 13.3 per 100,000 population. Cancer was the 3rd leading cause of premature death in Malaysia, however only 30-40% of all deaths from cancer are medically certified, meaning there is no exact figure of people dying from cancer (MOH 2008). Cervical cancer is the third most common cancer among female. It is 9.1 % of overall cancer in female. There were a total of 1074 cases of ICC with an ASR of 12.2 per 100,000 population. There were a lot to be improved compare to develope country like UK. Cervical cancer is the 12th most common cancer among women females in the UK (2010), accounting for around 2% of all new cases of cancer in females (National Cancer Registry scotland,Welsh, North Ireland 2012). Cervical cancer incident rate increased with age after 30 years old. It has peak incident rate at the

ages of 50-59 years and declined thereafter. This is so likely due to increased cancer incident with age itself. These features were very similar to data in 2002. Chinese women had the highest ASR of 28.8 per 100,000 population, follow by Indians with ASR 22.4 and Malay (ASR 10.5).(Malaysian Cancer Registry 2006).

In Kelantan cancer is the fourth cause of death. It come after infectious disease, respiratory disease and circulatory disease. Cervical cancer is the ninth most common cancer among Kelantanese population (JKN Kelantan 2008).

Aetiology and Associated Factor

There is much evidence demonstrating that HPV is a primary risk factor infact as the ethiology for cervical cancer and its plays a centrel role in its carcinogenesis (Ho et al, 1995; Remmink et al,1995; Nobbenhuis et al, 1999). High-risk oncogenic HPV types have been found to be associated with more than 99% of cervical cancers (Wabloomers JM Et al 1999). More than 70% of these cancers are linked to HPV 16 and HPV 18 genotypes (Smith JS et al 2007) . Types 16 and 18 are mostly found in cervical cancer and are transmitted by sexual contact (Rughooputh et al 2007). The proportion of women infected with HPV varies according to the women's age and among difference populations. It is estimated that 15-40% of young, sexually active women and 3-10% of women age 35 years of age or older are infected with HPV (M.V. Jacobs Et al 2000).

In the matter of fact that HPV is mostly transmitted via sexual contact, the other associated factor to cervical cancer is also related to sexual habit and HPV in particular. Overall, women who had first sexual intercourse at an early age or who have had many

sexual partners have an increased risk of developing cervical cancer. Apart from sexual behavior other co factor were smoking, nutrition, parity, immunodifficiency and oral contraceptive use have been reported as major environmental risk factors for cervical cancer. Smoking was shown to increased risk of cervical cancer by 2-5 fold. OCP associated with 1.6 fold of developing ICC most probably by increased in sexual activity. Patient with immunodificiency were more susceptible to developed ICC by the inability to clear of the HPV infection.(Shields T S et al 2004, Juneja A et al 2003)

Pathogenesis and the natural history of HPV is very important in the understanding the disease process. Most HPV infection was transient, about 80-90% goes off by the cell mediated immunity. This is true for low grade HPV infection. However in 10-15% of infection, especially by a high grade HPV, the infection is not irredicated. It persist for years. This group of women were those at risk of cervical cancer. Persistent infection with high risk HPV and the present of co factor will eventually transform the epithelial cell to neoplastic cell, CIN 2/3 which will lead to cervical cancer (Mc Credie MR et al 2008, Lu B et al 2009). The time taken from high risk HPV infection to develope CIN 3 is 3-5 years, progression to ICC take much longer ,estimated around 10-20 years (Mc Credie MR et al 2008) . In one study, 86.7 % of women with a positive HPV test did not develop cervical cancer or related premalignant disease after more than a decade of follow up (Chen HC 2011) .

Screening

Therefore cervical cancer screening should taking advantage of the long natural history of developing cervical cancer. Cervical Cancer screening must achieve three goals: to provide high coverage of the population at risk with an accurate screening test as a part of high quality services and ensure that women with positive result are properly managed (J Bradley Et al 2005).   Pap smear was first proposed by Dr George papanicolaou in 1940, many countries have significantly reduced their cervical cancer morbidity and mortality through cervical cancer screening and early treatment. In the United States, the introduction of the Pap smear has been responsible for a 90% decrease in deaths from cervical cancer.(Eddy DM 1990) . Likewise in Australia, deaths from cervical cancer have steadily decreased, at about 2.8% a year, since the introduction of the National Cervical Cancer Screening Program in 1991 (Free K et al 1991). While 75% of women in industrialized countries have been screened for cervical cancer, less than 5% have in developing countries (Memiah et al., 2012). Liquid-based Pap cytology is the preferred method of screening. Although intended to improve the accuracy of the Pap test, its main advantage has been to reduce the number of inadequate smears from approximately 9% to 1% . The test is also beneficial in testing for HPV dna (Diaz Rozario et al 1999 , Weintraub J & Morabia A 2002)

There were no standardization of pap smear practice and recommendation worldwide. American College of Obstetrician and Gynaecology (ACOG) in 2012 recommended pap smear screening to be done at the age of 21 -65 years old..no screening should be done prior to 21 years of age regardless of sexual practice. Patient with prior adequate and normal pap smear may stop screening at the age of 65. The frequency for screening

is 3 yearly tii 30 years old. Then 5 yearly till 65 years old. HPV testing should only be done after 30 years of age for screening purposes. Women in England and Northern Ireland (UK) are currently offered cervical cancer screening at three to five year intervals between ages 25 and 64. There was evidence that annual screening may produce only a minimally lower risk of invasive disease than screening every two to three years (USPSTF, 1996; Eddy M 1990). According to one study of eight cervical cancer screening programs in Europe and Canada, the incidence of cervical cancer can be reduced by 64 percent with a screening interval of ten years, by 84 percent with a five year interval, and by 91 percent, 93 percent and 94 percent with intervals of three, two and one years, respectively (IARC Working Group, 1986).

In Malaysia screening for cervical cancer,which almost exclusively mean conventional pap smear screening were provided by network of state-level health centres, the National Population and Family Development Board clinics, Federation of Family Planning Association clinics, private clinics/hospitals and university/teaching hospitals. The Pap smear screening programme was planned, organised and evaluated by the Ministry of Health, Malaysia (MOH 2008). Despite implementation of the national Pap smear screening program since 1969, only 26% of women had undergone screening in Malaysia (National Health and Morbidity Survey, 1996). This number does not really change much in recent year.

Presentation

The presentation were depend on the stage at presentation. Post coital bleeding (PCB) is the commonest symptom. However the positive predictive value of PCB for the diagnosis of cervical cancer in younger women is very low . Only 2% of patient with PCB will be diagnose ICC (Shapley et al 2006). In develope country (UK,Australia,New zealand) 70-90% presented in early stage, however under in developed country only 30-40 percent presented in early stage (IARC 2012)

Patern of Spread

Cervical cancer commonly spread locally to surrounding tissue. The Tumour may spread laterally to the parametrium, into the vagina, bladder and rectum. Invasion of tumour laterally may cause obstruction to the ureter and causing obstructive nephropathy and renal failure. Renal failure is a major cause of morbidity and mortality in ICC. Lymphatic spread is important as the lymph node metastasis is an independent prognosis for patient's survival. The tumour may also spread through blood stream to distant organs such as liver,spleen, kidney,lung,brain and bone (Shapley et al 2006, Dursun J et al 2007, Kodama J 2007).

Histopathological Subtype

WHO calcify ICC histology subtype into four category; Squamus cell carcinoma (SCC), Adenocarcinomas, Others carcinoma of cervix, and other malignant tumour of cervix. (Refer table 1 for detail). It has been estimated that around two thirds of cervical

cancers are squamous cell carcinoma (SCC) and around 15% are adenocarcinoma (with nearly all of the remainder of cases being registered as poorly specified) (Vizcaino AP et al 2000, Quinn M 2001). Cervical adenocarcinoma corresponds to less than 10% of invasive carcnomas. However the incidence of cervical adenocarcinoma has increased in recent decades particularly among young women (PG Chan Et al 2003). In Malaysia squamus cell carcinoma accopunt for 71.7% of cases , while adenocarcinoma 18.9% (National Cancer Registry 2003-2005). It is still a controvertial issue whether different cell types have different patterns of failure and survival to treatment. However some study shown adenocarcinoma of cervix had been shown to had poorer respond to treatment. It had a worse 5-year overall survival rate of 15–30% compared to SCC in all stages (Hopkins et al 1997).

Staging

Staging of cervical cancer that widely accepted is by FIGO staging. FIGO staging of cervical carcinoma is clinical and does not rely on surgico–pathological findings. This enables uniformity of staging for all patients worldwide. This is of particular importance because cervical carcinoma is most prevalent in countries where surgical and diagnostic resources are limited. This is also true enough as in advanced case staging laparatomy may be detrimental to subsequent radiation therapy and in some case might be inoperable . The first FIGO staging for cervical cancer was produced in 1928, since then it had been revised few time. The latest revised was in 2009. The clinical assessment may be supplemented by other investigations, such as examination under anesthesia, cystoscopy, sigmoidoscopy and intravenous urography, but these were optional and no longer mandatory under the new revised FIGO staging system 2009 (Perolli S 2009).

However, clinical staging has deficiencies in evaluating several parameters that are critical for treatment planning and prognosis of the patient. It is also noted to have a significant different when compare to surgicopathology staging in some study. For instant, compared with surgical staging, clinical FIGO staging can be erroneous in up to 32% of patients with stage IB disease and up to 65% of patients with stage III disease (Legase LD et all 1980 , Van NJ Junior et all 1979). In view of the lack in clinical staging FIGO continuosly encaurage the aid or use of MRI /PET scan along with the clinical staging. It had the advantage in diagnosing parametrial involvement, lymph node involvement, measuring of diameter of bulky tumour, metastatic disease (Local and distant) which is both important in management purposes and prognosis of patient (Perolli S 2009). MRI is now a widely used imaging modality in the initial staging of primary cervical cancer. It has been given an appropriateness criteria rating of 8 (out of 9) by the American College of Radiology (ACR) in the staging of invasive cervical cancer. The overall staging accuracy of MRI ranges from 77 to 90% (Subak et al 1995)

Prognosis

Prognosis for patient with ICC depends on the stage of the disease at diagnosis according to the International Federation of Gynaecology and Obstetrics Staging System (FIGO). (A Mohar and M.Frias-Mendivil 2000). Five year survival rate is 91.5% for stage 1, 83.5% for stage 2a, 66.5% for stage2b, 45% for stage 3a, 36% for stage 3b, and 14% for stage 4. Refer to Table 2. (Fletcher et all 2000). Depth of tumour invasion and lymphavascular space invasion and increased tumour volume or diameter is three independent prognostic factor for recurrent. Patient with tumour diameter < than 4cm with 2 lymph node postive had 10 years survival of 56-70%, while patient

with tumour diameter of >4cm with 2 positive nodes had survival of 13% in 10 years. (Trattner M et al 2001) Endometrial invasion assiociated poor prognosis and peritoneal carcinomatosis and increased distant metastasis (Gauthier P et al 1985, Dalgado G et al 1990). Patient with aggressive histology such as adenosquamus, small cell neuroendocrine, sarcoma, and poorly differentiated tumour were known for a poor prognosis (Kamura T et all 1992). Chung et al 1980 were one of the first to describe the importance of cervical invasion in prognosis and noted a significantly increased frequency of positive lymph nodes, recurrences and reduced 2-year survival rates when depth of cervical invasion is more than 70%. Parametrial involvement had been well studied to significantly affect the nodal metastasis incident and risk of recurrent. Patient with no parametrial involvement; 5 years survival rate 90-97%, patient with parametrial involvement had survival of 60-80% in 5 years (Bleker DP 1983, Boyce J 1981). There were few other factor that influence the prognosis such as age, general conditions and co morbidity and nutritional status. The effect of young age on survival in cervical cancer is not fully known, the association with aggrassive histology subtype and grade is a possible causes. Evidence has suggested that it is a poor prognostic factor and that young patients should therefore be treated differently from older patients. (Clive et al.1988).

Management

Early stage cervical cancer is stage 1a to stage 2a. This is because, there is room for both surgical and also oncology treatment. There is controversies of optimal treatment for early stage cervical ca with bulky tumour (>4cm), however in other group with early stage, surgery had more advantage in term of survival and avoidance of radiotherapy complication. Furthermore patient with cervical cancer tend to be young, rare comorbidity, sexually active and might still be in their reproductive age.

Early Stage

Early-stage carcinoma of the cervix is associated with a good prognosis. Five-year survival rates of stages I B and II A are 80-90% and 70-80% respectively. In several large series, stages I B and II A have been evaluated together and 5-year survival rates of approximately 80% were reported. Stage 1A1 had the risk of lymph node invasion of 0.5% without lymphovascular invasion .It is treatted with local excision cone biopsy or simple hysterectomy. Hovewer simple hysterectomy is the standard treatment is simple hysterectomy. Stage 1A2 , had the risk of nodal mets from 7- 10%. Pelvic lymphadenectomy is indicated. The surgery range from radical trachelectomy, modified radical hysterectomy to radical hysterectomy.

The risk of lymph node metastasis in stage 1b1 and 2A1 is 16-25%. The standard treatment is radical hysterectomy and pelvic lymphadenectomy. The aim of radical hysterectomy is to remove the tumour with adequate margin,including parametrium and upper part of vagina. The microscopic margin must be more than 5mm and pelvic node disection should include obturator, internal iliac, external iliac and common iliac lymph node. Class III radical hysterectomy consists of removal of the uterus and adjacent

parametrium to its most lateral extent, along the paracolpium and the upper portion of the vagina and the proximal uterosacral ligaments. Radical hysterectomy class II (modified radical hysterectomy) is equally effective as radical hysterectomy stage III, but with fewer side effect. Patient that treated primarily with radiotherapy and surgical had comparable outcome, survival rate of 75-100% (Landoni et al 1997). Theoretical advantages of primary surgical management may include; able to get more accurate staging information, removal of the primary tumor, thereby obviating the need for brachytherapy. In a few cases, surgery allows resection of bulky (2–3 cm) positive lymph nodes that are less likely to be sterilized with primary radiation (Hacker NF 1995). Detection of pathologic node involvement, allowing direction of adjuvant therapy. Although the overall survival of patients with stage IB1 cervical cancer treated by radical hysterectomy is excellent, patients frequently experience lower urinary tract dysfunction, sexual dysfunction, and colorectal motility disorders associated with autonomic nerve damage which is due to wide resection of the parametrium (Barnes W 1991, Magrina et al 1995,Bergmark K et al 1999) .

Patient with bulky tumour tumour of > 4cm largest diameter for stage 1B and 2A were further cathegorized to 1B2 and 2A2 (FIGO 2009 staging). Some author cathegorized this bulky tumour as locally advance cervical cancer as the prognosis is worse, incomplete surgical margin, lymph node involvement , risk of recurrent and overall survival (Allen D et all 2005). Comparision of stage 1B1 and 1B2 treated surgically shown significantly higher lymph node metastasis (28% versus 12.8%), paraaortic node involvement (8.1% versus 1.8%), parametrial involvement and need adjuvant radiotherapy in 52% versus 37% (Rutledge TL et al 2005). Due to all this fact and increased need for post operative adjuvant radiotheraphy, many oncologist prefer to

treat early bulky tumour with primary radiotherapy or chemoradiation. After primary surgical management, 50%-85% of patients with Stages IB2–IIA have indications for adjuvant radiation or chemoradiation. Morbidity is higher when surgery and radiation are combined (Landoni F et al 1997). Despite all the possible disadvantages, still no concrete evidence to support its as a superior approach in term of overall survival.

Late Stage

Stage 2B to 4 cervical cancer can be further devided to locally advanc (stage2B- 4A) and distant metastastic disease (stage 4B). The treatment intention for metastatic disease is paliative. For Locally advance disease the treatment is primary chemoradiation. In selected patient there is role of pelvic exantheration if the diseases not extending to the pelvic sidewall and no overt extrapelvic disease, particularly if a vesicovaginal or rectovaginal fistula is present (Shingleton HM et al 1989). However pelvic exanteration is rare taking into consideration of high intraoperative and post operative complication. According to a recent metaanalysis, concurrent Chemoradiatherapy, is the new standard treatment for locally advanced ICC (J.A Green 2001). Chemoradiation was shown to significantly improve the overall and progression free survival rates and reduce local and distant recurrence compared to radiation therapy alone. The addition of chemotherapy(Cisplatin or 5 Flurouracil) to radiotherapy treatment improved 5 years survival rate from 46-74% in stage 1B/ 2A. This is both achieved by reducing the rate of local recurrent and distant metastasis. For stage 3-4A disease, chemoradiation improved the 5 years survival rate from 45-59%, and disease free interval of 37% to 54% (Eifel PJ et al 2004).

Role of Adjuvant Radiotherapy or Chemoradiation post Surgery

In most centre, surgery is the treatment of choice for stage 1- 2A1 cervical cancer. Many patient that undergo primary surgical intervention did not require further treatment. Adjuvant radiotherapy or chemoradiation is required in a significant proportion of patient to reduce risk of recurrent. Indication for adjuvant therapy were lymph nodes metastasis, surgical margin less than 5mm, lower uterine segment involvement, parametrial infioltration, and aggressive histology subtype; adenosquamus, small cell neuroendocrine. The adjuvant radiotherapy or chemoradiation had shown to significantly reduce risk of recurrent. Even in the case of aggressive subtype the risk of recurrent were brought down 44 - 9 % (GOG 92 trial)

Radical Hysterectomy for Cervical Cancer

Wertheim reported the outcome of abdominal radical hysterectomy in 1912. Lymphadenopathy was not performed. However it was associated with high mortality and moorbidity rate. Meigs reintroduced radical hysterectomy with routine lymphadenectomy in 1951. Thus the current radical hysterectomy is a combination of Wertheim's and Meig's radical hysterectomy. The prosedure consists of removal of the uterus and adjacent parametrium to its most lateral extent, along the paracolpium and the upper portion of the vagina and the proximal uterosacral ligaments. Removal of Bilateral ovary is not mandatory, risk of ovarian metastasis with SCC is only 0.5% (sutton GP et al 1992). Radical Hysterectomy carries a high risk of bladder dysfuntion, anorectal dysfunction,sexual dysfunction likely due to nerve injury.