RESEARCH ARTICLE

Endometrial Cancer in Hospital Universiti Sains Malaysia

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Abstract

<u>Background</u>: Endometrial cancer is the most common gynecological malignancy among females worldwide, approximately 320,000 women being diagnosed with the disease each year and 76,000 dying. To date, there is limited knowledge of endometrial cancer in Malaysia. <u>Objectives</u>: To identify the epidemiological profile and prognostic factors of survival. <u>Materials and Methods</u>: A list of endometrial cancer patients in 2000-2011 was obtained from the hospital Record Department. Only cases confirmed by histopathology examination were included. We excluded those with incomplete medical records or referral cases. Simple and multiple Cox regression approaches were used for data analysis. <u>Results</u>: Only 108 cases were included with a mean (SD) age of 62.7 (12.3) years, with 87.0% Malay ethnicity. Grade of cancer was: 29.1% grade 1, 43.7% grade 2 and 27.2% grade 3. The majority of patients had non-endometrioid type (60.2%), with myometrial invasion (82.2%) and lymphovascular invasion (57.3%). The significant prognostic factors were age (HR 1.05; 95% CI: 1.02, 1.08, p=0.002) and having lymphovascular invasion (HR 2.15; 95% CI: 1.08, 4.29; p=0.030). <u>Conclusions</u>: Endometrial cancer patients should be diagnosed earlier to reduce the risk of mortality. The public should be given education on the signs and symptoms of the disease.

Keywords: Endometrial cancer - mortality - prognostic factors - Malaysia

Introduction

Endometrial cancer is the most common gynecological malignancy among females worldwide (Ferlay et al., 2010). It is an important cancer-related cause of death in women (Briet et al., 2005). Worldwide, endometrial cancer is the second most common gynecological cancer and the sixth most common cancer overall among women (Jemal et al., 2011). In Malaysia, National Cancer Registry reported that endometrial cancer contributed to 4.1% of total cancer cases involving women in 2007 (Zainal Ariffin and Nor Saleha, 2011). The local Kelantan Cancer Registry 1999-2003 reported that endometrial cancer falls into number eight of the most common cancers (Fauziah et al., 2006)

This study is a review of all cases of endometrial cancer admitted in Hospital Universiti Sains Malaysia (USM) in order to describe the epidemiological assessment and prognostic factors of survival. Our aim was to fill in the gaps of knowledge about endometrial cancer as there has hitherto not been much research related to this disease in Malaysia. By identifying the epidemiological profile and prognostic factors for survival, we can hopefully develop targeted strategies and activities for the early management of endometrial cancer in Malaysia.

Materials and Methods

This study was conducted at Hospital USM, which is located in Kubang Kerian, Kelantan, a north-eastern state in Peninsular Malaysia. It is a tertiary referral centre and the main provider of cancer care services in the area. A list of endometrial cancer patients admitted to Hospital USM in 2000-2011 was obtained from the Department of Records. We included only confirmed cases of endometrial cancer by histopathology examination in Hospital USM. We excluded those with incomplete medical record and referral cases.

A standardized checklist was extracted were age, race, diabetes status, menopausal status, type of cancer, grade of cancer, stage of cancer, parity, presence of myometrial invasion and presence of lymphovascular invasion. We also collected dates of when first symptoms related to endometrial cancer were noted, when the diagnosis was made, when the patient was last seen and death. Status of death was confirmed by the National Department of Registration. This study was granted ethical clearance for Research Ethics (Human) Committee USM.

Data entry and analysis was conducted using the Statistical Package for the Social Science (SPSS) version 22.0. Data distributions and frequencies (%) were

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examined. All continuous variables were expressed as the mean and standard deviation (SD) or as median and interquartile range (IQR), while categorical variables as frequency and percentage. Simple and multiple cox regression were used to determine the prognostic factors. Results are presented as hazard ratio (HR), 95% confidence interval (CI) and p-value. The level of significance was set at <0.05.

Results

There were 121 cases of endometrial cancer in the list from the Records Department, Hospital USM. However, 13 endometrial cancer patients had incomplete records, thus, only a total number of 108 patients were included in the final analysis. The majority of endometrial cancer patients (87.0%) were Malay ethnic. The mean (SD) age of endometrial cancer patients was 62.7 years (12.3). Table 1 shows the clinical feature of endometrial cancer cases in Hospital USM. Regarding the risk factors; 67.6% were menopause, 63.4% were nulliparous, and 39.8% had diabetes.

Table 1. Clinical Features of Endometrial Cancer Cases in Hospital USM (n=108)

	Frequency (%)
Diabetes Status	
No	65 (60.2)
Yes	43 (39.8)
Menopausal Status	
Premenopausal	35 (32.4)
Postmenopausal	73 (67.6)
Parity	
Multiparous	37 (36.6)
Nulliparous	63 (63.4)
Type of Cancer	
Endometrioid	43 (39.8)
Non-Endometrioid	65 (60.2)
Grade of Cancer	
1	30 (29.1)
2	45 (43.7)
3	28 (27.2)
Stage of Cancer	
I	25 (24.5)
II	11 (10.8)
III	27 (26.5)
IV	49 (38.2)
Myometrial Invasion	
No	18 (17.8)
Yes	83 (82.2)
Lymphovascular Invasion	
No	44 (42.7)
Yes	59 (57.3)

The majority of patients (60.2%) had non-endometrioid, and only 39.8% had endometrioid type of endometrial cancer. Tumours were in grade 1 (29.1%), 2 (43.7%) and 3 (27.2%) respectively. Most of endometrial cancer patients (64.7%) presented was in stage III and IV. More than half of patients (82.2%) had a myometrial invasion, and 57.3% had a lymphovascular invasion. The significant prognostic factors of endometrial cancer mortality in Hospital USM were age (HR 1.05; 95% CI: 1.02, 1.08, p=0.002) and having lymphovascular invasion (HR 2.15; 95% CI: 1.08, 4.29; p=0.030) (Table 2).

Discussion

The significant prognostic factors for endometrial cancer survival in our study were age and presence of lymphovascular invasion. The incidence of endometrial cancer will increase in line with the ageing of the female population and in elderly women, this cancer is more aggressive yet often undertreated (Renehan et al., 2004). The prognosis of endometrial cancer is grimmer in elderly patients (Renehan et al., 2004). It primarily occurs after the menopause which is similar to our study. Most of our patients were menopause when they diagnosed with endometrial cancer.

The lymphovascular invasion has been identified as an important risk factor for the progression of many neoplasms (Zaorsky et al., 2012). Lymphovascular space invasion is defined as the presence of tumor cells inside endothelium-lined channels of uterine specimens, outside the main tumor, and this pathologic finding is directly correlated with lymphatic tumor metastasis (Dos Reis et al., 2015). Dos Reis et al., (2015) also found that the presence of lymphovascular space invasion has been shown to be a predictor of lymph node metastasis and decreased survival in patients with endometrial cancer (Dos Reis et al., 2015).

The association of diabetes mellitus with the risk of endometrial cancer is well known (Dossus et al., 2010). In our study, diabetes mellitus is not a significant factor for endometrial cancer mortality. But the epidemiological study showed that mortality rate for cancer patients with pre-existing diabetes is moderately increased compared to non-diabetic patients (Fauziah et al., 2006). About 40.5% of our endometrial cancer patients had diabetes. A study by Jalil et al., 2015 reported that endometrial carcinoma patients showed the highest proportion being diabetics, as compared to other female cancer: ovarian cancer, breast carcinoma, and cervical cancer (Briet et al., 2005). In a large prospective study in Japan, patients with diabetes mellitus type 2 are at increased risk of

Table 2. Prognostic Factors of Endometrial Cancer Survival in Hospital USM (n=108)

	Simple Cox Regression			Multiple Cox Regression		
	b	Crude Hazards Ratio (95% CI)	P-value	b	Adjusted Hazard Ratio (95% CI)	P-value
Age	0.03	1.03 (1.01, 1.06)	0.013	0.05	1.05 (1.02, 1.08)	0.002
Lymphovascular Invasion						
No	0	1	-	0	1	-
Yes	0.58	1.79 (1.01, 3.15)	0.044	0.76	2.15 (1.08, 4.29)	0.03

total cancers (Ferlay et al., 2010). Meta-analysis studies found diabetes mellitus is significantly associated with endometrial cancer (Friberg et al., 2007). Studies showed that increased in 2-3 fold risk of endometrial cancer in patient with diabetes mellitus compared with the general population (Lindemann et al., 2008) and more than six-fold when associated with obesity (Friberg et al., 2007).

Hyperinsulinemia in diabetic patients promotes mammary carcinogenesis by increased IGF-1 level (Pavelic et al., 2007). IGF-1 exerts its mitogenic action by increasing Deoxyribonucleic Acid (DNA) synthesis and by stimulating the cyclin D1. Cyclin D1, in turn, lead to accelerated progression of cells cycle from G1 to S phase. IGF-1 also inhibits apoptosis to stimulate cell cycle progression in mutated cells (Yu and Rohan, 2000). Persistent chronic hyperinsulinemia and hyperglycemia in diabetes mellitus will lead to increase in IGF-1 level. IGFBP-rP1 also contributes to insulin resistance in human by competing to bind to the insulin receptor. IGFBP-rP1 has a higher affinity for insulin receptor (Lopez-Bermejo et al., 2006). High-level IGF-1 in the blood leads to increase in cell proliferation via the increase in cyclin D1 receptor and inhibit apoptosis of damaged cell via stimulation of BCL-2 gene (Renehan et al., 2004).

Cancer screening should be one of the steps to be instituted in diabetic clinics and diabetic screening in gynecology clinics. The risk of cancer development may also be lowered by these strategies. It is estimated that there would be 2.48 million diabetic patients in Malaysia by 2030 and Kelantan state is one with the highest prevalence in the country (Karageorgi et al., 2010). In a community where diabetes is prevalent, screening for epithelial cancers should be rigorous. Diabetic clinics should include screening for these cancers in their diabetic patients' follow-up protocol, and gynecology clinics should test for diabetes status of all women they see.

Higher FIGO stage was associated with greater endometrial cancer death rates (Jones et al., 2012). Tumour staging in our study was 22.5% stage I, 10.8% stage II, 24.3% stage III and 36.0% stage IV. Most of the patients with endometrial cancer usually seek early medical treatment in the early stage of the disease due to uncomfortable symptoms such as prevaginal and postmenopausal bleeding. In Malaysia, traditional healing is a common practice among cancer patients due to a few reasons such as a recommendation from family and friends, perceived benefit and compatibility, healer credibility, and reservation with western medicine. Delay in seeking medical treatment and interruption of treatment is often attributed to visiting traditional healers. Patients go to traditional healers with the expectation that the healer will treat their physical ailment. Some patients know or suspect they have cancer, and others may have painful physical symptoms causing distress, but have not yet been diagnosed with cancer. Since the patients seek traditional healers, they default their appointment.

Another reason for defaulted follow up is concerns about treatments and managing side effects, hospital stays, and medical bills. The patients may also worry about taking care of their family, keeping their job or continuing daily activities. The patients need regular checkups after being diagnosed with endometrial cancer. Checkups can help to ensure that any changes in health are noted and treated if needed. Checkups may include a pelvic examination, laboratory tests, chest x-ray, Computerized Tomography scan or Magnetic Resonance Imaging.

Endometrial cancer is a hormone related malignancy. Endometrial cancer mortality was higher for patients with non-endometrioid types than patients with endometrioid types (Jones et al., 2012). Our study also showed that endometrial cancer mortality was greater for patients with non-endometrioid endometrial cancer than patients with endometrioid type. Endometrioid type of cancer is closely related to excess estrogen and endometrial hyperplasia. Whereas non-endometrioid type of cancer is not associated with estrogenic cause and occur in atrophic endometrial (Emons et al., 2000). A study done in Japan demonstrated that estrodial induces proliferation of endometrial cancer cell via autocrine stimulation of IGF-1 mediated by mapk3/1 pathway (Kashima et al., 2009). The expression of IGF-2 and IGF-1R were much higher in malignant tissue of stages III and IV than in tumors of stages I and II and low in normal or hyperplastic endometrial (Pavelic et al., 2007).

Non-endometrioid endometrial cancers make up about 10% of all endometrial cancers but account for more than 50% of recurrences and deaths from endometrial cancer (Brinton et al., 2013). The most common non-endometrioid histology is papillary serous (10%), followed by clear cell (2% to 4%), mucinous (0.6% to 5%), and squamous cell (0.1% to 0.5%) (Mendivil et al., 2009). Serous carcinoma is an especially aggressive variant, with patients often presenting with stage II or III disease, deep myometrial invasion (40% to 50%), and frequent vascular invasion.

Patients with a higher grade of endometrial cancer had an increased risk of mortality (Jones et al., 2012). The study by Kauppila et al., 1982 stated that patients with grade 3 at all clinical stages had significantly lower survival rates than had patients with well-differentiated (grade 1) and moderately differentiated (grade 2) adenocarcinoma. The death of grade 1, grade 2 and grade 3 of endometrial cancer during the first two years occurred in 4.7%, 6.8%, and 18.2% of cases, respectively (Kauppila et al., 1982).

Our study showed that majority of patients (82.2%) had a myometrial invasion, and 57.3% had a lymphovascular invasion. Besides that, having lymphovascular invasion acted as a one of the significant prognostic factors for endometrial cancer mortality in Hospital USM. In patients with endometrial cancer, the depth of myometrial invasion correlates strongly with their survival. Myometrial invasion is spread of cancer to the myometrium which is the middle layer of the uterine wall. Lymphovascular invasion is considered to be an early step in the metastatic process and necessary for the progress of malignant tumours (Mannelqvist et al., 2011).

Endometrial cancer risk decreases with the greater number of full-term pregnancies (Schonfeld et al., 2013). Our study showed that 63.4% of endometrial cancer was nulliparous. Parous women are 20% to 40% less likely than nulliparous women to develop endometrial cancer (Dossus et al., 2010; Karageorgi et al., 2010). The exact mechanism by which parity reduces risk is

not known, but several hypotheses have been proposed. Elevated progesterone levels during pregnancy may inhibit estrogen driven endometrial cell proliferation and promote the differentiation and apoptosis of endometrial cells (Henderson and Feigelson, 2000). Vaginal delivery itself or the postpartum involution of the uterus may facilitate the shedding of precancerous or cancerous cells in the endometrial lining of the uterus (Baird and Dunson, 2003). Certain infertility conditions, such as anovulatory disorders, that lead to nulliparity also may contribute to higher endometrial cancer risks among nulliparous women (Brinton et al., 2013).

There were some limitations in this study. Reviewing medical records has some inherent weaknesses such as missing variables, in particular, socio-economic details and blood investigations. Our study was also a single-centre study; thus, the results may not be generalized; however, we believe that this is the first review of endometrial cancer mortality in Malaysia.

In conclusion, early detection will reduce the number of death of endometrial cancer patients. Besides that, relatives and friends should play a role to motivate and encourage the relatives or friend who suffers from endometrial cancer. The awareness of the symptoms, risk factors and associated factors of endometrial cancer mortality should be spread widely not only print media but through television, radio and online network should be active from time to time. The health programme about endometrial cancer should be carried out in open places to give more information about endometrial cancer to the public.

Acknowledgements

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