Original Article

Median Survival Time of Endometrial Cancer Patients with Lymphovascular Invasion at the Hospital Universiti Sains Malaysia

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Abstract

***Background*: Endometrial cancer is the most common gynaecologic malignancy among females worldwide. The purpose of this study was to determine the median survival time of endometrial cancer patients at the Hospital Universiti Sains Malaysia (USM).**

***Methods*: A list of 121 endometrial cancer cases registered at Hospital USM between 2000 until 2011 was retrospectively reviewed. The survival time of the endometrial cancer patients was estimated by Kaplan-Meier survival analysis. Log-rank tests were performed to compare the survival of the patients based on socio-demographics and clinical presentation.**

***Results*: Only 108 patients, 87.0%, were included who were of Malay ethnicity. Previous history included menopause in 67.6% of patients and diabetes mellitus in 39.8% of patients; additionally, 63.4% of patients were nulliparous. Tumour staging was as follows: 24.5% stage I, 10.8% stage II, 26.5% stage III and 38.2% stage IV. The overall median survival time of the endometrial cancer patients was 70.20 months (95% confidence interval (CI): 51.79, 88.61). The significant factors were age, the presence of lymphovascular invasion and treatment received.**

***Conclusion*: The overall survival of endometrial cancer was low. A prospective study needs to be carried out to discover more effective and accurate tests for the early detection of endometrial cancer.**

Keywords: *endometrial carcinoma, female, retrospective study, Kaplan-Meier estimate, Malaysia*

Introduction

Endometrial cancer is the most common gynaecologic malignancy in the United States (1) with 54,870 new cases expected and 10,170 deaths estimated in 2015 (2). Worldwide, endometrial cancer ranks as the second most common gynaecological cancer and the sixth most common cancer overall among women (3). In Malaysia, the National Cancer Incidence reported that endometrial cancer contributed to 4.1% of all cancer cases involving women in 2007 (4).

Endometrial cancers are classified into two broad histologic types: type I (endometrioid) and type II (non-endometrioid). The mortality was higher for patients with type II rather than patients with type I (5) because type I cancers are more likely to grow and spread outside the uterus. However, this type is only presented in 20% of all endometrial cancer cases, which consists of less common histological subtypes such as serous carcinoma, clear cell carcinoma and carcinosarcoma (6). Although endometrioid types are more common in endometrial cancer patients (80%–85% of all cases) (6), they are not

very aggressive and are slow to spread to other tissues.

This study was conducted to determine the median survival time of endometrial cancer patients at the Hospital Universiti Sains Malaysia (USM). Until recently, most studies on endometrial cancer have been conducted in countries other than Malaysia. Therefore, this problem needs further investigation concerning the factors involved so that the findings may improve the survival of endometrial cancer patients. The results of this study may help to develop targeted strategies and activities for early management and to guide future studies.

Materials and Methods

This study was conducted at the 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. The study design was a retrospective cohort in which the patients' medical records were reviewed retrospectively. This study involved patients diagnosed with endometrial cancer at the Hospital USM between January 2000 and December 2011. We included only cases of endometrial cancer confirmed by histopathology examination at the Hospital USM. Cases with more than 30% incomplete data and referral cases were excluded.

A total of 121 endometrial cancer patients were subsequently identified. After screening for inclusion and exclusion criteria, 108 patients were eligible for this study. All data were extracted and recorded on a data extraction sheet. A single researcher retrieved the required information.

A standardised checklist was used to extract 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 the dates of when the first symptoms related to endometrial cancer were noted, when the diagnosis was made, and when the patient was last seen, as well as the date of death. Status of death was confirmed by the National Department of Registration. This study was granted ethical clearance by the Research Ethics (Human) Committee USM.

Data entry and analysis were conducted using SPSS version 22.0 for Windows (7). Survival analysis was performed, and the outcome factor was survival time, defined as the time to death of patients due to endometrial cancer or its complications. This study used censored observation when patients survived beyond the end of study period, became untraceable or were lost to follow-up. Death from high blood pressure, stroke, asthma, septicaemic shock and anaphylactic shock were also considered censored cases. The significance of the censored data being considered in the analysis was to avoid under estimation of survival time.

The survival probability of patients with endometrial cancer was estimated using a univariable method, the Kaplan-Meier product limit method. The survivor function or the Kaplan-Meier survival curve was used to determine the 50th percentile (the median) of survival time and to compare the survival distributions of two or more groups. The survival curves of the groups were compared using log-rank tests. For independent variables with more than two groups, multiple pairwise comparisons produced cumulative type I errors. The Bonferroni correction was applied to α; the value was divided by a number of pairs compared (α/number of pair compared) (8). The *P*-value obtained was compared to the corrected α to determine the significance level.

Results

Table 1 shows the socio-demographics of the endometrial cancer patients at the Hospital USM. The majority of patients (87.0%) were of Malay ethnicity, and 83.3% of them were greater than 50 years old. Table 2 shows the clinical presentation of the endometrial cancer patients. Regarding the risk factors, 67.6% were post-menopause, 63.4% were nulliparous, and 39.8% had diabetes mellitus.

Most of the patients presented with non-endometrioid cancer (60.2%); only 39.8% had endometrioid endometrial cancer. Tumours were in grade 1 (29.1%), 2 (43.7%) and 3 (27.2%). A total of 64.7% of patients were stage III and IV. Among all endometrial cancer patients at the Hospital USM, 82.2% had myometrial invasion, and 57.3% of patients had lymphovascular invasion. All patients received a total abdominal hysterectomy and bilateral salpingo-oophorectomy surgery. Of 108 patients, 68 (63.0%) received both chemotherapy and radiotherapy after surgery.

Table 1. Socio demographic of endometrial cancer cases in Hospital USM (n = 108)

		Patient's Status		
		Died n (%)	Censored n (%)	Total n (%)
Age (years)	50 and below	4 (7.3)	14 (26.4)	18 (16.7)
	Above 50	51 (92.7)	39 (73.6)	90 (83.3)
Ethnicity	Malay	48 (87.3)	46 (86.8)	94 (87.0)
	Chinese	7 (12.7)	7 (13.2)	14 (13.0)

Table 2. Clinical presentation of endometrial cancer cases in Hospital USM (n = 108)

		Patient's Status		
		Died n (%)	Censored n (%)	Total n (%)
Diabetes Status	No	31 (56.4)	34 (64.2)	65 (60.2)
	Yes	24 (43.6)	19 (35.8)	43 (39.8)
Menopausal Status	Premenopausal	13 (23.6)	22 (41.5)	35 (32.4)
	Postmenopausal	42 (76.4)	31 (58.5)	73 (67.6)
Parity	Multiparous	19 (35.2)	18 (38.3)	37 (36.6)
	Nulliparous	35 (64.8)	29 (61.7)	64 (63.4)
Type of Cancer	Endometrioid	16 (29.1)	27 (50.9)	43 (39.8)
	Non-Endometrioid	39 (70.9)	26 (49.1)	65 (60.2)
Grade of Cancer	1	11 (21.2)	19 (37.3)	30 (29.1)
	2	28 (53.8)	17 (33.3)	45 (43.7)
	3	13 (25.0)	15 (29.4)	28 (27.2)
Stage of Cancer	I	11 (21.2)	14 (28.0)	25 (24.5)
	II	5 (9.6)	6 (12.0)	11 (10.8)
	III	17 (32.7)	10 (20.0)	27 (26.5)
	IV	19 (36.5)	20 (40.0)	39 (38.2)
Myometrial Invasion	No	6 (11.3)	12 (25.0)	18 (17.8)
	Yes	47 (88.7)	36 (75.0)	83 (82.2)
Lymphovascular Invasion	No	18 (33.3)	26 (53.1)	44 (42.7)
	Yes	36 (66.7)	23 (46.9)	59 (57.3)
Treatment Received	None	15 (27.3)	14 (26.4)	29 (26.9)
	Radiotherapy	6 (10.9)	5 (9.4)	11 (10.2)
	Chemotherapy and radiotherapy	34 (61.8)	34 (64.2)	68 (63.0)

The median follow up of endometrial cancer patients at the Hospital USM was 10 months. The overall median survival time measured in this study was 70.20 months (95% CI: 51.79, 88.61). Figure 1 illustrates the median survival time of endometrial cancer patients at the Hospital USM based on the presence of lymphovascular invasion. The log-rank test was used to compare survival between age groups, lymphovascular invasion groups and treatment groups (Table 3).

For the age groups, a significance difference was observed between the age of 50 years old and younger compared to greater than 50 years old (P = 0.041). For the lymphovascular invasion groups, a significant difference was observed between the endometrial cancer patients with lymphovascular invasion and without lymphovascular invasion (P = 0.042). For the treatment groups, a significance differences were seen between the patients who did not receive any treatment and the patients who received radiotherapy (P = 0.046), as well as between the patients who received radiotherapy and the patients who received both chemotherapy and radiotherapy (P = < 0.001).

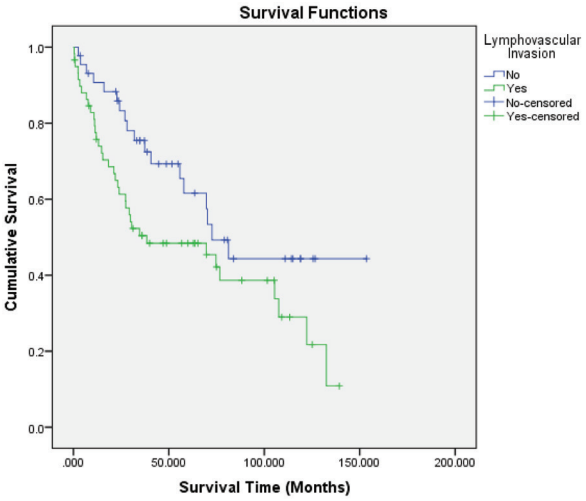

Figure 1. Kaplan-Meier estimates of survival time of endometrial cancer patients at the hospital.

Discussion

The incidence of endometrial cancer increases steadily with age. The older the age at which the endometrial cancer is diagnosed, the greater the risk of death from endometrial cancer. Endometrial cancer primarily occurs after menopause, with a mean age of 68 years at diagnosis. With the ageing of the female population, the incidence of endometrial cancer will increase (9). The present study showed that non-endometrioid cases accounted for more than half (60.2%) of patients, with 64.7% of patients presenting with advanced stages.

Type I and type II endometrial cancer are considered biologically distinct disease entities that are characterised by their divergent histologies, molecular genetics, tumourigenesis, and clinical behaviour. Different patterns of molecular alterations are now thought to underlie the pathogenesis and/or progression of type I and type II endometrial cancer (10, 11). For example, the most common genetic alterations in type I cancer include microsatellite instability and mutations of *PTEN*, β-catenin, *PIK3CA*, and *K-ras* (12). In contrast, in the case of type II cancer, *p53* mutations are common (11), and ERBB2 (formerly HER2) overexpression or amplification is also frequently observed (13).

Our study reported that the overall median survival time of endometrial cancer patients was 70.20 months. However, the median survival in our study is lower than the medial survival reported in Thailand in 2010 (14) and higher than that reported in Madrid, Spain in 2013 (15). Several prognostic factors have been shown to be predictors of survival in patients with endometrial cancer. Tumour stage, tumour grade, histological type, and depth of myometrial invasion were defined by the International Federation of Gynecology and Obstetrics (FIGO) as prognostic factors for endometrial cancer (16). However, lymphovascular invasion is not included among the prognostic factors of the 1988 FIGO surgical staging classification (1, 13). Although lymphovascular invasion is not included, once it occurs, tumour cells have the potential for metastatic spreading to other sites.

In our study, the presence of lymphovascular invasion was the most significant prognostic factor for survival. More than half of the patients (57.3%) had lymphovascular invasion. Vascular or *lymphatic* system *invasion* occurs when endometrial cancer cells break into blood vessels or lymph channels. The incidence of lymphovascular invasion is higher in serous and clear cell types, but it may be present in any cell type. Lymphovascular invasion is reported in 3 to 34% of endometrial cancers (17), and it is a common event in tumour progression and distant dissemination of disease (18).

Table 3. The median survival time of endometrial cancer cases in Hospital USM (n = 108)

		Median Survival Time	
		Median	95% CI
Age (years)	50 and below	-	-
	Above 50	69.60	39.21, 100.99
Lymphovascular Invasion	No	72.60	56.59, 88.62
	Yes	38.47	0.00, 81.99
Treatment Received	None	72.60	13.98, 131.22
	Radiotherapy	11.14	4.38, 17.89
	Chemotherapy and Radiotherapy	74.74	29.97, 119.50

Lymphovascular invasion was an independent predictor of both decreased overall survival (19) and disease-related survival in patients with stage I-III endometrial cancer (20). It also has been described as a predictor of lymph node metastases, since the risk of spread to lymph nodes is known to be higher in patients with lymphovascular invasion (1). A study by Zhang et al. (21) reported that the presence of lymphovascular invasion in patients with stage I or II endometrial cancer had a sensitivity and specificity of 41.7% and 94.5%, respectively, to predict pelvic lymph node metastasis.

The presence of tumour cells within endothelial-lined spaces is a strong predictor of recurrence and death (22, 23). Prat (24) stated that stromal retraction is a frequent artefact that may stimulate vascular invasion. Immuno-peroxidase staining of endothelial cells (factor VIII or CD31) may facilitate the recognition of vascular channels (25). A perivascular lymphocytic infiltrate is often associated with vascular invasion. Vascular invasion is infrequent in endometrioid carcinomas; the frequency of vascular invasion increases with unfavourable cell type, high histological grade, and deep myometrial invasion (24). Nevertheless, the presence of vascular invasion is highly suggestive of lymph node metastases (22, 26).

Different types of treatments are available for endometrial cancer patients. All endometrial cancer patients in our study were treated primarily with surgery, undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection. Chemotherapy and radiotherapy may follow surgery. However, the treatment depends on the tumour stage, histologic grade and depth of myometrial invasion. The majority of our patients received both chemotherapy and radiotherapy after surgery. This finding is because a greater number of patients had lymphovascular invasion with advanced stage and higher grade.

Pelvic external beam radiotherapy has been the standard adjuvant treatment for patients with high-risk endometrial cancer for several decades (27). Randomised trials comparing adjuvant chemotherapy and external beam radiotherapy showed similar rates of survival (28, 29). A trial that investigated a combination of external beam radiotherapy with two cycles of cisplatin, followed by four cycles of cisplatin-paclitaxel in 46 patients with high-risk endometrial cancer showed the four-year overall survival was 85%, and disease-free survival was 81%. Another trial that compared external beam radiotherapy alone with external beam radiotherapy and four cycles of platinum-based chemotherapy showed statistically significantly improved progression-free survival with the addition of chemotherapy (30). The previous finding was similar to the current study, which showed that patients treated with a combination of radiotherapy and chemotherapy had longer survival times than those treated with radiotherapy alone. However, a comparison between pelvic radiotherapy alone and vaginal brachytherapy followed by three cycles of carboplatin and paclitaxel in patients with stage I–II endometrial cancer with high-intermediate-risk or high-risk features and with a median follow-up of 24 months showed no difference in overall survival (31).

Reviewing medical records has 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 generalised; however, we believe that this is the first review of endometrial cancer mortality in Malaysia.

Endometrial cancer does not have a recognised screening programme in Malaysia and many countries worldwide. Awareness about endometrial cancer should be increased among the Malaysian population, especially with regards to common presenting symptoms and risk factors. Endometrial cancer represents a considerable challenge to the clinician. Advances are needed that will allow surgery to be performed safely in a specialist centre on patients who are fit for surgery.

It is important that patients take meticulous care of themselves before, during, and after cancer treatment. Taking care includes eating well to get the right amount of calories to maintain a healthy weight. Patients also need enough protein to keep up their strength. Sometimes, especially during or soon after treatment, the patients may not feel like eating. The patients may be uncomfortable or tired and may find that foods do not taste as good as they used to. Additionally, the side effects of treatment, such as poor appetite, nausea, vomiting, or mouth blisters can make it difficult to eat well. The patients need regular check-ups (every three to six months, for example) after treatment for endometrial cancer. Check-ups can help to ensure that any changes in health are noted and treated if needed.

A diagnosis of endometrial cancer can change a patient's life and the lives of those close to him/her. These changes can be difficult to handle. It is normal for the patients and their family and friends to require help in coping with the feelings that a diagnosis of cancer can bring. Concerns about treatments and managing side effects, hospital stays, and medical bills are common. The patients may also worry about caring for their family, keeping their job or continuing daily activities.

Conclusion

The overall survival of endometrial cancer was low. A prospective study needs to be conducted to discover more effective and accurate tests for the early detection of endometrial cancer so that patients can be diagnosed at earlier stages, before symptoms of endometrial cancer, such as loss of appetite and pleural effusion, arise. This will lead to a better survival outcome for endometrial cancer patients and reduce mortality rates.

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Conflict of Interest

None

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Authors' Contribution

Conception and design: S-AAH, AAMZ, NHO
Analysis and interpretation of the data: S-AAH, WNAWA
Drafting of the article: S-AAH, WNAWA
Critical revision of the article for important intellectual content: NHO
Final approval of the article: AAMZ, NACJ, NHO
Provision of study materials or patients: NACJ
Statistical expertise: S-AAH, WNAWA, NHO
Obtaining of funding: AAMZ, NACJ
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