ORIGINAL ARTICLE

Preoperative Serum CA 125 is Associated With Myometrial and Cervical Invasion in Endometrial Carcinoma

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ABSTRACT

Introduction: Endometrial carcinoma is the most common gynaecological malignancy in developed countries and the sixth most common cancer among women worldwide. Cancer staging is vital in treatment decisions and the prediction of prognoses, and is based on imaging studies, histological results and surgery. Therefore, a simple and fast preoperative tool to predict the precise cancer stage of patients is needed. CA 125, a cancer antigen, is used in assessing therapeutic response and cancer surveillance in endometrial carcinoma. However, this tumour marker is not routinely performed in the mentioned circumstances. Studies have shown that preoperative CA 125 was significantly high in patients in a higher stage of endometrial cancer. Thus, this study aims to assess the primary role of CA 125 in predicting the stage of endometrial carcinoma, by correlating preoperative serum CA 125 with clinicopathological parameters. **Method:** The retrospective data of endometrial carcinoma cases consisting of demographic and clinicopathological parameters as well as preoperative serum CA 125 levels were retrieved from Laboratories Information System (LIS) at Hospital Selayang, Selangor, Malaysia, from January 2000 until June 2016. Only 20 cases fulfilled the inclusion and exclusion criteria. Preoperative serum CA 125 was correlated with demographic and clinicopathological parameters, and was analysed using a Kruskal-Wallis test. **Results:** There was a significant association between elevated serum CA 125 with myometrial and cervical stroma invasion in endometrial carcinoma ($p<0.05$). **Conclusion:** Preoperative serum CA 125 is a useful marker in predicting early stages of endometrial carcinoma, and plays a role in pre-operative cancer staging in endometrial carcinoma.

Keywords: CA 125 Antigen, Endometrial carcinoma, Endometrium cancer, Cancer staging, Neoplasm invasiveness

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INTRODUCTION

Endometrial cancer

Endometrial carcinoma is a malignant tumour that arises from the endometrial lining of the uterus. It is the most common gynaecological malignancy in developed countries (1). In Malaysia, endometrial cancer is the 6th most common cancer in females, accounting for 4.6%, 4.0% and 4.1% in the Malay, Chinese and Indian population respectively (2). Endometrial carcinoma typically occurs in elderly patients, 80% of who are in the postmenopausal age. It is less common among patients under the age of 40. In the latter age group, endometrial carcinoma may be familial, which is associated with Lynch syndrome or is sporadic (3).

There are a number of risk factors that may contribute to this malignancy, including obesity, diabetes mellitus, hypertension, infertility, failure of ovulation, long standing oestrogen usage, and some degree of endometrial hyperplasia (4). Most of these conditions are associated with unopposed estrogen. Oestrogen increases the mitogenic activity of the endometrial glandular epithelium (5). Diagnosis of endometrial cancer is made primarily by physical and microscopic examination of the endometrial sampling in symptomatic patients. In the United Kingdom, both endometrial biopsy and transvaginal ultrasound are used in conjunction during the diagnosis. Other imaging modalities such as CT scan and MRI are also used mainly for investigating extrapelvic or distant sites the disease has spread.

Screening of asymptomatic patients is rarely performed. However, women with family history and at who are at a high risk of developing cancer are encouraged to undergo screening.

In 1988, the International Federation of Gynaecology and Obstetrics (FIGO) implemented a surgical staging system for endometrial cancer, which was later updated in 2009, to guide in patients' management and prognostication (6). FIGO stage 1 is defined when the tumour is limited to the endometrium, invades less than half of the myometrium (stage IA), or invades half or more of the myometrium (stage IB). FIGO stage II is when the tumour invades the cervical stroma, but does not extend beyond that. FIGO stage III is defined when there is local and/or regional metastasis, where it is divided into stage IIIA (the tumour invades the serosa of the corpus uteri or adnexae), stage IIIB (vaginal involvement or parametrial involvement) and stage IIIC (any tumour category in stage I-III with presence of pelvic lymph node metastasis without distant metastasis). In terms of FIGO stages I, II, IIIA and IIIB, there is an absence of lymph node metastasis and distant metastasis. Finally, FIGO stage IV is defined when any tumour category in stage I-III is present, the presence or absence of pelvic/paraaortic lymph node and the presence of distant metastasis.

Apart from poor prognosis, myometrial invasion is also a factor that determines the need of adjuvant therapy. One particular study suggested that gross evaluation of hysterectomy specimen was 82% accurate for myometrial invasion (7). However, 3% of women with less than half of myometrial invasion by endometrial malignancy were also reported to have nodal metastasis. Therefore, gross myometrial invasion cannot be used as a total predictive of nodal metastasis.

Assessment of cervical stroma involvement is part of the new FIGO revised criteria for staging of endometrial cancer (8). Involvement of cervical stroma is defined as stage II. The presence of cervical invasion has a greater risk of advanced disease such as extra uterine spread and lymph node metastasis. Preoperative diagnosis of cervical involvement is essential to determine an appropriate treatment for patients. The preoperative modalities that were found to be useful are cervical cytology and radiological imaging, especially magnetic resonance imaging (9,10).

The mainstay of endometrial cancer treatment is surgery (11). About 90% of women with endometrial cancer are treated by total hysterectomy with bilateral salphingo-oopherectomy (TAHBSO) and/or lymphadenectomy (removal of pelvic and para-aortic lymph nodes), depending on the stage they are in. The five year survival rate for endometrial adenocarcinoma following appropriate treatment is 80% (4).

Serum CA 125

Cancer antigen or carbohydrate antigen (CA) 125, a cancer antigen, is a soluble glycoprotein that is produced by tumour cells or by the body in response to tumour cells. The level of CA 125 has been used clinically for cancer surveillance and therapeutic monitoring in ovarian and endometrial cancer. This particular antigen is present in human cells such as mesothelial cells and in Mullerian epithelium derivatives such as the fallopian tube, and endometrial and endocervical cells. Other pathological conditions that may cause elevation of CA 125 include pancreatic, colorectal cancer and metastatic cancer. The serum concentration is mostly proportional to tumour size. There are also benign conditions that may potentially cause elevation of this antigen, including endometriosis, pelvic inflammatory disease (PID), pregnancy, menstruation, ascites and pancreatitis. CA 125 can also be higher in healthy women who are less than 49 years old. A retrospective study in Taiwan has shown that preoperative CA 125 significantly increased in patients with advanced stage, larger tumour size, deeper depth of invasion, cervical involvement, adnexal involvement, positive nodes and peritoneal fluid cytology (12).

Although there are no simple laboratory tests that have been found to assist in diagnosing endometrial cancer, serum CA 125 has been used in monitoring therapeutic response and surveillance of the disease, but histopathological examination remains the gold standard investigation for the diagnosis.

Several recent studies have shown that high serum CA 125 concentration is also a risk factor for poor prognosis (13). Very high level of serum CA 125 is a sign that the disease may have spread beyond the uterus. Many studies have come out with reference cut-off values for serum CA 125 level, but the selection of the appropriate value for clinical use needs to be analysed carefully. A study involving 112 endometrial cancer patients showed elevated serum CA 125 levels above 35 U/ml in 15.2%, 33.3%, 61.5%, and 100% patients with stage I, II, III and IV respectively. This shows a good correlation between serum CA 125 and cancer stage (14).

Serum CA 125 level was also used to monitor cancer response to treatment. Serum CA 125 level >35 U/ml was detected in relapse cases, and only 5% of disease-free cases showed increased CA 125 level postoperatively (15).

Serum CA 125 is raised in some percentage of endometrial carcinoma, but is not routinely performed. It plays a limited role in endometrial carcinoma, such as in assessing therapeutic response and cancer surveillance. A simple and fast preoperative test to predict cancer stage is needed to assist in treatment

decisions and prognostication, apart from the standard radiological, histological and surgical assessments. Furthermore, a similar study is lacking in the context of Malaysia. Thus, this study aims to assess the role of serum CA 125 in predicting the stage of endometrial carcinoma by correlating preoperative serum CA 125 with clinicopathological parameters.

MATERIALS AND METHODS

The retrospective data of confirmed endometrial carcinoma cases consisting of demographic (i.e. age and race) and clinicopathological parameters (i.e. histology type, histology grade, cancer stage, myometrium invasion, positive or negative cytology, adnexal involvement, cervical stroma invasion, lymph node metastasis and distant metastasis) as well as preoperative serum CA 125 were retrieved from the Laboratories Information System (LIS) at Hospital Selayang, Selangor, Malaysia, from January 2000 until June 2016.

According to Kirkwood formula (2003) for estimated sample size calculation, 99 cases were required for this study. However, only 20 cases fulfilled the inclusion and exclusion criteria during the mentioned study period. The inclusion criteria comprised patients with confirmed diagnosis of endometrial cancer by histological examination, with complete staging after undergoing hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or periaortic lymphadenectomy, washing cytology, and without a history of chemotherapy or radiotherapy. The baseline level of serum CA 125 must be performed prior to any operation (preoperative) or treatment in the centre the study was conducted. The serum CA 125 was performed using ADVIA Centaur CA 125II assay, which measures the concentration of CA 125 up to 600 U/mL, with a minimum detectable concentration of 2 U/mL. The cut off value of serum CA 125 is 34 U/ml. The ADVIA Centaur CA 125II assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses two monoclonal mouse antibodies specifically for CA 125. Cases with concurrent conditions that may cause false elevation of serum CA 125 such as endometriosis, adenomyosis, ovarian primary tumours, pelvic inflammatory disease (PID), pancreatitis, or pancreatic or colorectal cancer, were excluded from the study. These concurrent conditions were assessed and excluded based on clinical, radiological, histological and blood investigation findings. Validity and reliability of serum CA 125 and histopathology reports were according to the standard operating procedure (SOP) of pathology laboratory and external quality assurance programme.

The results were analysed using standard statistical software package IBM SPSS statistics, SPSS version 22.0. Nonparametric Kruskal–Wallis H test was used to evaluate the relationship between CA 125 with demographic and clinicopathological parameters, since the data of serum CA 125 levels was not in a standard normal distribution. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and clinicopathological distribution

From among the 20 cases, 18 (90%) cases were aged 50 years old or over, and two cases (10%) were less than 50 years old (mean age is 57). Among the ethnic groups, Chinese was the highest, which comprised eight (40%) cases, followed by Malay, Indian and other races, which comprised seven (35%), four (20%) and one (5%) case(s) respectively. In terms of stage, cases in FIGO stage I were the highest, followed by stage III, stage II and lastly stage IV; at ten (50%), seven (35%), two (10%) and one (5%) case(s) respectively. As for tumour grades, FIGO grade 2 showed the highest, with 11 (55%) cases; followed by grade 3, with six (30%) cases; and grade 1, with three (15%) cases. Among all types of endometrial carcinoma, the majority was endometrioid adenocarcinoma, with 15 cases (75%); followed by endometrioid adenocarcinoma with squamous differentiation, with four cases (20%); and others, with one case (5%) (Table I).

The value range of serum CA 125 in the studied cases was 4.5 U/ml to 477 U/ml (mean level 62 U/ml). The cut off level for serum CA 125 was 34 U/ml. Eleven cases (55%) have elevated serum CA 125 level while 9 cases (45%) showed a non-elevated level. In 18 patients aged $\geq$ 50 years old, 11 cases (61%) showed elevated serum CA 125 while all two patients <50 years old showed a non-elevated level. The elevated levels were seen in 50% of the cases for each Chinese and Indian and 43% of Malay cases. The majority of cases with elevated levels were FIGO stage III (6; 55%) (mean level 65 U/ml), followed by stage I (3; 27%) (mean level 62 U/ml), and stages II and IV (1; 9 % for each). For histological grade, the elevated levels of serum CA 125 were highest (83%) (mean level 125.4 U/ml) in grade 3; followed by grade 2 (55%) (mean level 77 U/ml). All three cases of grade 1 showed a non-elevated level. For histological type, the elevated level of CA 125 in endometrioid adenocarcinoma cases and endometrioid adenocarcinoma with squamous differentiation cases comprised of 53% and 50% respectively. One particular case with a positive cytology showed an elevated level and 53% of cases with a negative cytology had an elevated level. For cases with adnexal involvement, the elevated level of serum CA 125 comprised 75% of the cases. As for lymph node metastasis, the elevated levels of serum CA 125 were seen in all cases (mean level 178 U/ml), while for only one case with distant metastasis, the elevated level was 477 U/ml. Among 10 cases

Table I : Association between preoperative serum CA 125 with demographic and clinicopathological parameters

Parameters		No. of cases (%) n=20	Median (IQR) CA 125 level (U/ml)	Z statistic	P value#
Age (years)					
	<50	2 (10)	7.70 (-)		
	≥50	18 (90)	46.75 (52.88)	1.638	0.101
Race					
	Malay	7 (35)	7.50 (53.20)		
	Chinese	8 (40)	53.45 (68.93)		
	Indian	4 (20)	36.95 (46.25)	1.389	0.576
	Others	1 (5)	-+		
Histology type					
	Endometrioid adenocarcinoma	15 (75)	43.10 (53.70)		
	Endometrioid adenocarcinoma with squamous differentiation	4 (20)	32.95 (359.90)		
	Others	1 (5)	-+	0.4	0.861
FIGO grade					
	1	3 (15)	10.90 (-)		
	2	11 (55)	45.00 (56.50)		
	3	6 (30)	50.80 (128.85)	0.482	0.233
FIGO stage					
	I	10 (50)	8.25 (53.75)		
	II	2 (10)	52.40 (-)		
	III	7 (35)	48.50 (15.30)	1.659	0.102
	IV	1 (5)	-+		
Myometrium invasion					
	>1/2	10 (50)	9.95 (48.28)		
	≥1/2	10 (50)	53.45 (62.20)	2.192	0.028*
Positive cytology					
	Yes	1 (5)	-+		
	No	19 (95)	43.10 (53.30)	0.607	0.544
Adnexal involvement					
	Yes	4 (20)	98.95 (359.00)		
	No	16 (80)	30.25 (52.55)	1.795	0.073
Cervical stroma invasion					
	Yes	8 (40)	55.75(84.58)		
	No	12 (60)	9.95(48.90)	2.39	0.017*
Lymph node metastasis					
	Yes	4 (20)	96.65 (349.50)		
	No	16 (80)	23.15 (52.55)	1.795	0.073
Distant metastasis					
	Yes	1 (5)	-+		
	No	19 (95)	43.10 (52.70)	1.648	0.99

#Kruskal Wallis test (Mann-Whitney U test was not significant); -+omitted (because CA 125 level was constant); *Statistically significant ($p < 0.05$)

each with superficial (stage IA) and deep myometrium invasion (stage IB), three (30%) (mean level 59 U/ml) and eight (80%) (mean level 121 U/ml) cases showed elevated CA 125 levels respectively. As for eight cases with cervical stroma invasion (stage II), seven of them (87.5%) had an elevated serum CA 125 level (mean level 131 U/ml). For stage IB, at 34 U/ml cut off CA 125 level, the calculated false positive rate, false negative rate, specificity and sensitivity was 30%, 20%, 70% and 80% respectively. Meanwhile, for stage II tumour, at 34 U/ml cut off CA 125 level, the calculated false positive rate, false negative rate, specificity and sensitivity was 33%, 12.5%, 67% and 87.5% respectively.

Association between preoperative serum CA 125 with demographic and clinicopathological parameters

When assessing the association between preoperative serum CA 125 and demographic and clinicopathological parameters, only myometrial invasion ($p = 0.028$) and cervical stroma invasion ($p = 0.017$) showed a significant association with preoperative serum CA 125.

DISCUSSION

Older age groups are more likely to acquire endometrial carcinoma and postmenopausal state is one of the contributing factors in the histogenesis of the endometrial cancer. This fact was supported by this study and other studies, where the percentage was higher in women aged 50 years or older (16,17). This study did not show any significant association between serum CA 125 and age, which concurred with several studies (18,19,20). The study showed that the Chinese population was predominant as compared to other races, which differed from a local study where the Malay population was found to the most common. The reason might be because of the small sample size, and the fact that the samples were collected from a single institution which might not be representative of the entire population.

As for tumour grade, this study showed similar findings with a local study conducted in 2016, where the percentage was highest in grade 2, followed by grades 1 and 3. However, their findings differed for tumour stage, where most of their cases presented at later stages (stage III and IV) (16).

In this study, the mean value of preoperative serum CA 125 (62 U/ml) was similar to one particular study (13), where the mean value was 63.5 U/mL (range 6.1–677.0 U/mL) and was higher compared to two related studies (12, 21), which were 43.6 U/mL (range 1–1899 U/mL) and 28.5 U/mL (range 7 to 151 U/mL) respectively. The percentage of cases with elevated serum CA 125 level in this study was higher (55%) in comparison to one large study which comprised of 23.5% with CA 125 cut off value > 35 U/mL (12). This might be due to the smaller sample size of this study. The elevated levels of serum CA 125 were high in poor prognostic factors such as FIGO stage III (mean level 65 U/ml), FIGO grade II and III (mean level 77 and 125.4 U/ml respectively), adnexal involvement (mean level 225 U/ml), lymph node metastasis (mean level 178 U/ml), deep myometrial invasion (mean level 59 U/ml) and cervical stroma invasion (mean level 131 U/ml). The findings were in accordance with many related studies (12, 19-24).

Previous studies also reported that raised preoperative serum CA 125 levels were strongly correlated with high stage and grade of endometrial carcinoma, deep myometrial invasion, cervical stromal invasion and lymph node metastasis (12,19,20,23). The findings of this study are partly in line with the above studies. The interesting finding in this study is the significant association between elevated serum CA 125 in early stages of endometrial carcinoma involving myometrial and cervical stroma invasions (stage I and II); while no significant association was seen in late stage parameters of endometrial carcinoma, involving lymph node and distant metastasis (stage III and IV). This may suggest that preoperative CA 125 is a useful tumour marker in predicting early stages of endometrial carcinoma, and may result in a better prognosis. However, the findings need to be validated, as the sample size was relatively small. The presence of cervical invasion has a greater risk of advanced disease. It is associated with extra uterine spread and lymph node metastases. Preoperative diagnosis of cervical involvement is essential in determining the appropriate treatment for patients, and this study supported this.

The study could not determine the cut off value of serum CA 125 level to predict myometrium or cervical stroma invasion, as the study sample was small for the statistical analysis to be valid. A study (12) had come out with a cut off value serum CA 125 to determine myometrium invasion, which was 18.25 U/ml (62.8% sensitivity, 63.9 % specificity). Atguden et al. (2016), in their study of 136 cases, involving only endometrioid type endometrial carcinoma, concluded that 16 U/ml cut off value (67% sensitivity, 66 % specificity) may potentially be used as a predictive test in patients with early stage endometrioid-type endometrium (25). In this study, the calculated sensitivity (80%) and specificity (70%) for deep myometrium invasion at 34 U/ml cut off value was also high. As for cervical stromal invasion, 22 U/ml (69.7% sensistivity, 70.4 % specificity) and 41.9 U/ml (87.5% sensistivity, 87.8 % specificity) cut off levels were suggested by another two studies (12,24). The findings in this study were similar to the two studies, where the calculated sensistivity and specificity for stage II tumour at 34 U/ml cut off value were 87.5% and 67% respectively. However, the cut off value for both early stages (stage I and II) need to be validated in a larger scale study.

Several studies have also come out with various cut off values of serum CA 125 to predict other clinicopathological parameters in endometrial carcinoma. Yildiz et al. (2012) suggested that serum CA 125 cut off level of 20IU/ml may be useful to predict the stage of endometrial carcinoma (22), 50U/ml to predict positive peritoneal cytology and >35U/ml as a cut off value for the indication of lymphadenectomy (21). Another study suggested a 30 U/ml cut off value for stages III and IV (12). Preoperative serum CA 125 is an important predictor for patients with endometrial cancer when determining the surgical management, especially in performing lymphadenectomy in patients with clinical stage I.

CONCLUSION

A significant association between preoperative serum CA 125 level with myometrium and cervical stroma invasion suggest that it is a useful marker in predicting early stages of endometrial carcinoma, and plays a role in preoperative cancer staging of endometrial carcinoma. Therefore, preoperative serum CA 125 may be a useful clinical tool for predicting prognosis and planning for the optimal management in patients with endometrial carcinoma. However, the preoperative cut off value of CA 125 level to predict the myometrium and cervical invasion could not be determined due to the small sample size used in this study. For future work, a similar study should be carried out prospectively with a larger sample size from multiple health centres across Malaysia, in order to validate the findings of this study on early stage endometrial carcinoma, and to come out with the cut off levels of preoperative serum CA 125. The findings might be useful in detecting early stages of endometrial carcinoma.

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