

CA125 Asa Predictor for Lymph Node Metastasis in Endometrial CancerAbdulrahim Gari^{1,2,3}, Hatim AlJefri¹, Rami Khalifa¹, Sabah Allarakia¹, Khulood Hussein⁴¹ National Guard King AbdulAziz Medical City, Jeddah, KSA.² Department of Obstetrics & Gynecology, College of Medicine-Umm AlQura University, Makkah, KSA..³ Department of obstetrics & Gynecology, King Faisal Specialist Hospital and Research Center, Jeddah, KSA.⁴ Department of Physiology, College of Medicine-King AbdulAziz University, Jeddah KSA.gari505@yahoo.ca

Abstract: Background: Endometrial cancer is the most common gynecological tumor. Previous studies have shown that there is a controversy regarding the preoperative predictive role of CA125 as a serum marker for the lymph node metastasis and prognosis of endometrial cancer. The current study aims at adding more evidence for the predictive role of CA125 for lymph node metastasis among patients with endometrial cancer. **Methods:** A retrospective study of all patients with endometrial cancer who had been operated in the National Guard Hospital in Jeddah - Saudi Arabia in the period from 2004 to 2014 (n=80). The pre-operative serum level of CA125 was evaluated for all the patients and the postoperative lymph node evaluation was recorded for 53 patients. In addition to the description of the clinical and demographic characteristics of the patients, Fisher exact test was carried out to find out the association between CA125 level, staging of the tumor and treatment modalities. **Results:** The majority of the patients who were operated for endometrial cancer were fifty years old or older (83.7%), these patients were mostly obese (82.5%) and multiparous (62.5%). Slightly more than one-half were diabetic (52.5%) and 50% were hypertensive. Serum level of CA125 exceeding 35 U/ml was detected in 13.8% of the patients, a significantly higher proportion of the patients who had CA125>35 U/mL (36.4%) than patients who had CA125<35 U/mL (7.2%) were discovered later to have an advanced stage of the tumor (3 or 4) p<0.05. Regarding treatment modalities, most of the cases with CA125>35U/ml needed extra measures such as radiotherapy or chemotherapy after being operated by TAHBSO with Lymphadenectomy. **Conclusion:** Endometrial cancer is more common among elderly, obese, diabetic females with a positive family history of cancer. Preoperative serum cutoff level of CA125>35 U/ml could predict prognosis and seriousness of the cases in terms of advanced stage and treatment modalities.

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Keywords: Endometrial cancer, CA125, Lymph nodes

1. Introduction

Worldwide, endometrial cancer is the seventh malignant disorder with a varying incidence along different regions⁽¹⁾, it is considered the most common gynecological malignancy in the Western world⁽²⁾, the incidence is still increasing due to prolonged life expectancy, changes in reproductive behavior, obesity as well as the (unopposed) use of hormone replacement therapy (HRT)⁽³⁾. In patients with endometrial cancer, it is important to identify pre-operatively those who are a low risk for metastases, who do not need radical surgery and lymphadenectomy⁽⁴⁾. The ability to predict lymph node metastasis preoperatively potentially enables primary care physicians to refer patients at high risk to centers with the surgical expertise required for proper staging and possible enrollment in studies of new treatment protocols for preventing lymph nodes recurrences⁽⁵⁾. Serum tumor markers have a major role in the screening, diagnosis, and monitoring of most of the gynecologic cancers (Kobayashi, *et al.*,

2012). For gynecologic cancers, only a small handful of tumor-associated antigens, such as CA125, have been routinely used as tumor markers. The precise role CA125 in the preoperative evaluation of the endometrial cancer patient remains less defined, possibly even controversial. Elevated levels of CA125 in patients with advanced stage and recurrent endometrial cancer have been reported⁽⁶⁾. The benefit of preoperative serum CA-125 levels in selected uterine cancer patients such as high-risk early stage uterine cancer patients may identify those patients with early stage disease who are more likely to benefit from lymphadenectomy, i.e., requires full surgical staging⁽⁷⁾. In the medical literature, data on the preoperative evaluation of the risk of lymph node metastases in endometrial cancer in the Saudi population are lacking. The aim of this study is to evaluate the correlation of preoperative serum CA 125 levels and staging of the tumor in Saudi women with endometrial cancer.

2. Methods:

This a retrospective study, as we reviewed the medical records of all endometrial carcinoma patients operated in the Princess Nora Oncology Center at National Guard hospital in Jeddah city-Saudi Arabia between 2004 and 2014. The preoperative serum CA 125 level was tested for all patients, and a value of 35 U/ml was selected as a cutoff level. All the surgical specimens were examined at the Department of Pathology of our institution, surgical staging of the tumor was based on the criteria of the International Federation of Gynecology and Obstetrics (FIGO) system ⁽⁸⁾. This study was approved by the ethical committee of the hospital. Results are presented mainly in descriptive form. Due to a violation of conditions for Chi-square test, Fisher exact test was used instead to find out the significant association between CA125, both the staging of the tumor and treatment modalities. *P*-value < 0.05 was considered as statistically significant. All analysis was performed using SPSS Version 20.0.

3. Results:

The records of 80 patients with endometrial cancer who were operated in the period between 2004-2014 were reviewed. Most of the patients (83.7%)

were aged more than fifty years, the great majorities were either overweight (13.8%) or obese (82.5%) and almost two-third (62.5%) were multiparous [Table1]. One-half of the patients were diabetic (52.5%) and another one-half were hypertensive (50.0%). Positive family history of cancer was detected in seven patients (8.8%), out of them, six (7.5%) had a family history of breast cancer and one (1.3%) of uterine cancer. Clinically, as shown in table 2, CA125 level exceeding 35 was detected in 11 patients(13.8%). Almost three-quarters of the patients (72.6%) were staged as stage 1, mostly as stage 1A (37.5%) or stage 1B (32.6%). Almost one-half of the patients undergone Total Abdominal Hysterectomy Bilateral Salpingo Oophorectomy (TAHBSO) alone (45%) or combined with radiotherapy (47.5%) as an adjuvant treatment.

Table 3 shows that a significantly higher proportion of the patients who had CA125>35 U/mL (36.4%) than patients who had CA125<35 U/mL (7.2%) were discovered later to have an advanced stage of the tumor (stage 3 or 4) *p*<0.05. Moreover, only a few minority of the patients who had CA125>35 U/mL had undergone TAHBSO alone (18.2%), otherwise, they need either radiotherapy or chemotherapy (81.8%) if compared to only one-half of the patients with CA125>35U/mL, (*p*=0.052).

Table 1. Characteristics of the patients (n=80).

Characteristics	No.	%
Age categories:		
<50 years	13	16.3
50-70 years	53	66.2
>70 years	14	17.5
BMI categories:		
Within normal	3	3.8
Overweight	11	13.8
Obese	66	82.5
Comorbidities:		
Diabetes mellitus	41	52.5
Hypertension	40	50.0
Family history of cancers:		
Breast cancer	6	7.5
Uterine	1	1.3
None	73	91.2

Table 2. Clinical characteristics of the endometrial cancer (n=80).

Clinical characteristics	No.	%
CA125 level:		
≤35 years	69	86.2
>35 years	11	13.8
Stage:		
T1	2	2.5
T1a	30	37.5
T1b	26	32.6
T2	13	16.3
T3a	3	3.8
T3b	3	3.8
T4	3	3.8
Management:		
TAH BSO* alone	36	45.0
TAH BSO* and Radiotherapy	38	47.5
TAH BSO* and chemotherapy	4	5.0
Chemotherapy alone	2	2.5

* TAHBSO Total Abdominal Hysterectomy Bilateral Salpingo Oophorectomy

Table 3. Staging and management of endometrial cancer patients according to preoperative level of CA125.

Management of patients	CA125 level		P value*
	CA125<35	CA125>35	
Stages 1 or 2	64(92.8%)	7(63.6%)	0.018
Stages 3 or 4	5(7.2%)	4(36.4%)	
TAHSO alone	34(49.3%)	2(18.2%)	0.052
TAHBSO with radiotherapy or chemotherapy	35(50.7%)	9(81.8%)	

* Based on Fisher exact test

4. Discussion:

Endometrial cancer is considered as the commonest uterine cancer, despite the exact etiology is not been well known, yet; there are several suggestions pointing out to the association between its occurrence and other comorbidities. For example, it had been stated that increased body weight either in the form of overweight or obesity is associated with chronic hyperinsulinemia and insulin resistance, which has significant implication on the occurrence of cancers, including endometrial cancer⁽⁹⁾, which supports the findings of our study which revealed that the great majority of our patients were either overweight (13.8%) or obese (82.5%). In the same line, hyperinsulinemia and hyperglycemia are thought to promote carcinogenesis in diabetic patients⁽¹⁰⁾. Diabetes has been associated with a statistically significantly increased risk of endometrial cancer in most, but not all studies, the notion that had been asserted by Friberg *et al.* through a meta-analysis of case-control studies and cohort studies⁽¹¹⁾, which

comes in congruence with the findings of our study where more than one-half of the patients were diabetic. Endometrial cancer commonly occurs among elderly women, most of the cases occur usually between the ages of 60 and 70 years but a few cases may occur before age 40⁽¹²⁾, in our study, most of the patients (83.7%) were aged more than fifty years. Despite the protective effect of pregnancies against endometrial cancer⁽¹³⁾, a lot of epidemiological studies have reported that nulliparous women have more endometrial cancer risk than multiparous⁽¹⁴⁾, this protective effect decreases at an advanced age, especially among grand multiparous patients who are usually diagnosed at an advanced age. However; the duration since last birth might be a factor in the risk of endometrial cancer⁽¹⁵⁾. We found in our study that almost two-thirds of the cases were multiparous. The early appearance of symptoms of endometrial cancer explains why most of the cases are categorized as early stages⁽¹⁾, this notion supports our findings which

revealed that most of our cases were staged as either stage 1A or stage 1B.

Although several researches have suggested that the preoperative measurement of CA125 is useful for predicting advanced stages of endometrial cancer and lymph nodes metastasis. The accuracy of the cutoff level has been considered as a matter of debate⁽¹⁶⁾. For example, several authors suggested a lower cutoff level of CA 125 (20 U/ml) as a more preoperative serum predictor for the extra-uterine spread of endometrial⁽¹⁶⁻¹⁸⁾. Other studies have also suggested that an age-stratified cutoff level for CA125 (35 U/mL in patients >49 years old and 105 U/mL in patients ≤49 years old) can improve the prognostic stratification of patients with endometrial cancer⁽¹⁹⁾. In our study where the cut-off level for CA125 was set at 35 U/mL, a level exceeding 35 was detected in 11(13.8%) of the patients, the significant role of CA125 in predicting the stage of endometrial cancer detected in our study supports the findings of previous studies, as Hsieh et al in (2002) addressed that a preoperative CA125 level can be considered as an indication for complete surgical staging of endometrial cancer⁽²⁰⁾, hence the referral to gynecologic oncologist. The results pertaining to the treatment modalities needed for our patients with a high CA125 level >35, which adds to the previously suggested indicator; that preoperative higher level of CA125 could predict advanced stage and the prognosis of endometrial cancer^(7;16).

Conclusion:

Endometrial cancer mostly occurs among elderly and obese females, diabetes and positive family history of cancer are additional risk factors. Preoperative serum cutoff level of CA125 >35 U/ml could predict advanced disease and the need for post-op adjuvant treatment. The current study could not provide enough evidence for its effectiveness in predicting lymph node metastasis. A larger number of patients probably are required to prove the value of preoperative CA125.

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