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Validity of CA-125 in the Diagnosis of Absent Lymph Node Metastasis in Endometrial Cancer Patients

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Abstract

Background: Serum CA 125 is elevated in many physiological and pathological conditions that are related to endometrial proliferation as menstrual cycle, pregnancy, endometriosis, and endometrial carcinoma. Many researchers studied Serum CA 125 level and its role in the assessment of endometrial cancer patients. The relation between the CA 125 level and many variables was demonstrated, such as lymph node involvement, myometrial invasion, disease stage, and overall survival. ***Aim***: to evaluate the relation between the tumor marker CA 125 and lymph node metastasis. ***Patients and Methods:*** A total number of twenty-six patients with endometrial carcinoma were enrolled in the study. Serum CA 125 was withdrawn preoperatively to all patients. The patients were subjected to total abdominal hysterectomy and bilateral salpingo-oophorectomy. A method of lymphatic mapping using patent blue dye was performed. The sentinel lymph node(s) and non-sentinel lymph nodes were sent for H&E staining. ***Results:*** On evaluating serum CA-125 of ≤35 IU/mL in predicting the absence of lymph node involvement as confirmed pathologically, the sensitivity was 87%, specificity 100%, positive predictive value 100%, negative predictive value 50% with accuracy 88.5%. ***Conclusion:*** CA 125 is a valid method in the preoperative assessment of patients with endometrial carcinoma.

Keywords: CA 125, Sentinel Lymph Node, Lymphatic Mapping, Endometrial Carcinoma.

Introduction

Serum CA 125 is a mucin glycoprotein that can be detected using the monoclonal antibody OC 125. It is also known as Carbohydrate Antigen 125 or Cancer Antigen 125. It can be detected in all humans and present in mesothelial cells of the pericardium, pleura, peritoneum, and derivatives of Mullerian epithelium such as endometrial, tubal, and endocervical cells[(1)]. There is no consensus about the cutoff value of CA 125 level to diagnose endometrial carcinoma. Some authors use levels as those used in ovarian cancer patients. The association between the serum CA-125 and the endometrial cancer stage was assessed in 254 patients. More

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patients with advanced-stage endometrial cancer (stage III and stage IV) were found to have serum CA 125 level > 35 U /L (58%) when compared with those with early-stage (16%)[2]. The ability of CA 125 to predict adnexal involvement was challenged and a cutoff value of serum CA125 level of 30 U/mL had a sensitivity of 84.6% and specificity of 84.3% in predicting adnexal involvement in endometrial cancer. This is in agreement with the role of CA 125 in detecting ovarian malignancy[3]. In a trial to use immunohistochemical markers and CA 125 level, a model was generated using serum cancer antigen 125 (CA125) level, the progesterone receptor (PR), and Ki67. Low-risk patients for lymph node metastasis included patients with serum CA125 < 30.0 IU/mL, either or positive PR staining > 50%, and Ki67 < 40% in cancer lesions. The negative predictive value of that model was 97.4%. Its sensitivity was 84.6% and its specificity was 67.4%. These results supposed that this model can be used as a guide in the prediction of lymph node involvement[4]. The rationale of this study is to evaluate the relationship between CA 125 and endometrial cancer.

Patients and Method

This is a diagnostic self-controlled study conducted on patients with endometrial cancer in the department of General Surgery, Suez Canal University Hospital, Ismailia, Egypt in the period between September 2019 and October 2021. The study protocol was revised and approved by the local ethical committee of the faculty of medicine and informed consent was obtained from each patient. Patients diagnosed with endometrial cancer stages (I/II) by MRI were enrolled in the study. Excluded from the study were patients unfit for operation. All included patients were subjected to detailed medical history, full general examination, and thorough abdominal examination. Liver function tests, chest radiographs, Pelviabdominal US, and pelvic MRI were performed to exclude distant metastasis. At least 1 ml of serum is collected in a red-top tube stored at room temperature for testing CA 125. Once the patient was under anesthesia, an exploratory laparotomy was performed, and the tumor was identified. The peritoneum over pelvic spaces was mobilized carefully. Then; lymphatic mapping was performed using 1–2 ml of isosulfan blue dye (Patent Blue, 2.5% Guerbet laboratories, France). The dye was injected sequentially into the subserosa of the uterus (Figure 1). After a few minutes (5-10 min), the pelvic spaces were examined for blue-stained LNs (Figures 2 & 3). The primary tumor and its draining lymphatic basin containing the non-SLNs were processed histologically in the standard fashion with H&E staining. Each SLN was cut into sections and stained with H&E.

Statistical Analysis

Data from history, operative findings, laboratory results of CA 125, and pathological assessment of LNs (after H&E staining) were analyzed by statistical package for social science SPSS 20 (SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as mean and standard deviation while qualitative data are expressed as numbers and percentages of the total.

Results

The study included 26 patients with early-stage endometrial cancer. Table 1 shows the age of the studied patients ranged

between 46 to 80 years with a mean age of 62.47 ± 8.43. BMI ranged between 25 to 42 with a mean of 34.16 kg/m^2. Forty-six percent of studied patients had hypertension while diabetes accounted for (26.9%) of the studied patients. About 20% of patients had more than one comorbid disease. The pathological examination of the preoperative specimen revealed a higher prevalence of the endometrioid type (88.5%) and grade I tumor (73.1%). More than half of the studied patients had grade I tumors. The endometrioid type was predominant (88.5%). About 69% of them had myometrial invasion less than 50%. Two patients had cervical involvement. 11.5% had lymph node involvement.

Table 1: Demographic and clinical characteristics of endometrial cancer patients:

Variables	**Range**	**Mean ± SD**
Age (years)	46 – 80	62.47 ± 8.43
BMI (kg/m^2)	25 – 42	34.16 ±4.77
Parity	0 – 7	2.68 ± 1.69
Medical history	**Number (N=26)**	%
Free	8	30.7
DM	5	26.9
HTN	10	46.2
Others	3	19.2

Table 2: Association between preoperative serum CA125 and pathological factors in endometrial cancer patients

	CA-125 level				**Test of significance**	
	≤ 35 IU/mL		**>35 IU/mL**		χ^2	**p**
	N=20	%	**N=6**	%		
Grade						
• I	12	60	4	66.7	0.65	0.723
• II	6	30	2	33.3		
• III	2	10	0	0		
Type						
• Endometrioid	18	90	5	83.3	3.957	0.138
• Serous	0	0	1	16.7		
• Mixed mullerian	2	10	0	0		
Myometrial invasion						
• 0 - < 50%	16	80	2	33.3	Fisher	0.03*
• > 50%	4	20	4	66.7		
Cervical involvement	0	0	2	33.3	Fisher	0.01*
Distant metastasis	0	0	1	16.7	Fisher	0.2368
LN metastasis	0	0	3	50	Fisher	0.01*
Stage						
• I – II	20	100	3	50	Fisher	0.01*
• III - IV	0	0	3	50		

and tumor grade, tumor type, or distant metastasis. On evaluating serum CA-125 of ≤35 IU/mL in predicting the absence of lymph node involvement as confirmed pathologically, the sensitivity was 87%, specificity 100%, positive predictive value 100%, and negative predictive value 50% with an accuracy of 88.5%.

The number of excised LNs ranged from 7 to 24 with a median of 12. There was a statistically significant relation between the high level of CA-125 and deep myometrial invasion, higher disease stage, and cervical and lymph node involvement. There was a statistically non-significant difference relation between CA-125 level

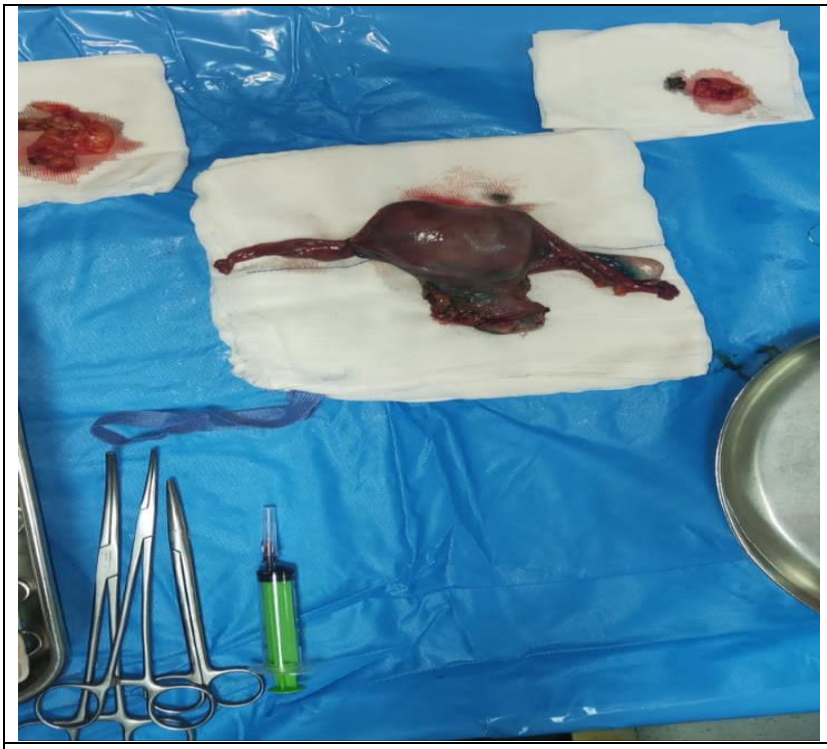

Figure 1: Total abdominal hysterectomy with sentinel LNs (Rt and Lt)

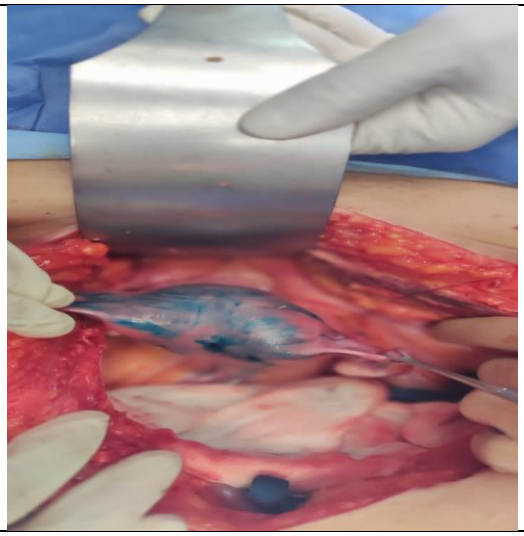

Figure 2: Patent blue dye subserosal injection

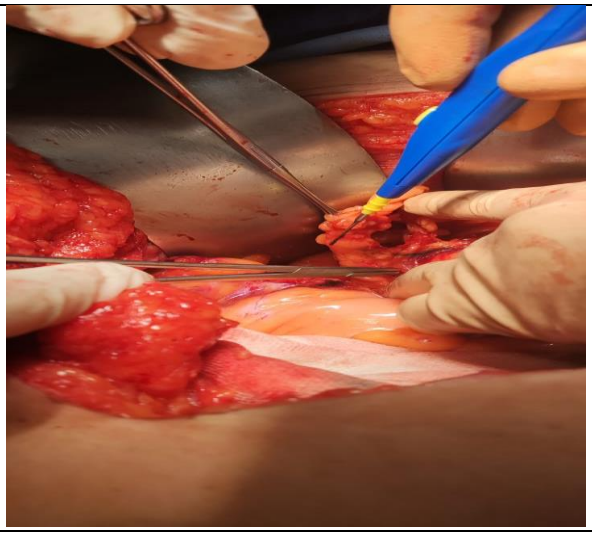

Figure 3: Lt pelvic LNs excision

Discussion

This study included 26 patients with early-stage endometrial cancer patients. Blood samples for CA 125 assessment were collected. Sentinel lymph node mapping was done using patent blue dye. The majority of studied patients in the current study had grade I tumors (61.5%) with a predominance of endometrioid type (88.5%) followed by serous and mixed mullerian types. Le and his group[5] also found higher final tumor grade in 22.6% of patients and a change of the histologic type to non-endometroid type was found in 5.3% of patients. The discordance between the preoperative tumor grade and the grade of the final specimen may be an obstacle in determining low-risk patients preoperatively. This may justify the need for some sort of lymph node assessment in endometrial cancer patients, even those who were diagnosed preoperatively to be of low-risk disease. In our study, most cases were diagnosed to have stage I disease (22 cases, 84.6%).

Table 3: Validity of CA-125 (≤35) in the diagnosis of absent lymph node metastasis in endometrial cancer patients:

CA-125	LN involved		Total
	No	Yes	
≤35	20	0	20
>35	3	3	6
Total	23	3	26

Sensitivity	Specificity	PPV	NPV	Accuracy
87	100	100	50	88.5

The high prevalence of early-stage endometrial cancer in the current study is justified by the exclusive selection of early-stage disease, diagnosed based on clinical and imaging findings, to be enrolled in the study. However, upstaging that occurred in 3 cases (11.5%) means that preoperative workup can't accurately detect the disease stage. Surgical staging is mandatory. Eighteen out of the 26 patients with early-stage endometrial cancer, who were included in the current study, had their lymph nodes stained yielding a detection rate of 69.2%. Comparing our results with other studies, Eitan et al.[6] performed robotic surgical staging, which yielded an overall detection rate of 62.1%. Approximate overall detection rates were reported by another two studies. One performed staging laparotomy (61% detection rate). The other study performed laparoscopic and robotic surgical staging (64.4% detection rate). Higher detection rates were reported in another two studies. One of them was performed by laparoscopy (overall detection rate of 83%). The other one was performed by robot-assisted surgery (overall detection rate of 75%). Higher detection rates in laparoscopic and robot-assisted surgery were justified by the rapid access to pelvic spaces and wide and magnified view[7]. In our study, there was a statistically significant relation between CA 125 level and myometrial invasion, lymph node involvement, tumor stage, and cervical involvement. Other parameters such as tumor grade, tumor type, and distant metastasis showed a statistically insignificant relation. The absence of a relation between CA 125 level and tumor

grade can be explained by the fact that undifferentiated endometrial cancer tissues exhibit less positive CA 125 staining[8].

Conclusion

CA 125 is an important tool in the assessment of endometrial cancer.

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