The accuracy of preoperative serum CA-125 levels to predict lymph node metastasis in a population of South African women with endometrial carcinoma

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Background: The purpose of the study was to evaluate the predictive value of serum CA-125 levels in the preoperative assessment of endometrial carcinoma in a setting where late presentation is common.

Method: This retrospective study evaluated women with pathologically proven endometrial carcinoma scheduled for surgery between January 2012 and January 2017, who had preoperative serum CA-125 test results. The association of CA-125 with a variety of histological factors was evaluated using Spearman's correlation and receiver operator characteristic (ROC) curves to evaluate sensitivity and specificity.

Results: Fifty-eight patients were included in the study, 34 (58.6%) of whom were FIGO stage II–IV. Elevated CA-125 levels were significantly correlated with late FIGO stage ($p < 0.001$), myometrial invasion ($p < 0.001$) and lymph node metastases ($p < 0.001$). The most appropriate cut-off point of CA-125, where an increase in sensitivity was not associated with a fall-off in specificity, was 20 IU/ml, reaching a sensitivity of 90% and a specificity of 67% for detection of lymph node metastases.

Conclusion: Among this group of women with endometrial cancer, the preoperative serum CA-125 level was associated with lymph node metastases and we found a CA-125 of 20 IU/ml or more to be predictive. These findings suggest that, among similar populations, CA-125 could be done preoperatively and could be used to determine the need for node dissection. Since our findings are from a small retrospective cohort, this should be validated in a prospective study on early stage disease.

Keywords: CA-125, endometrium carcinoma, lymph node metastases, surgical management

Introduction

Endometrial carcinoma is the sixth most frequent cancer in women and frequently diagnosed in women aged 55–64 years. It was estimated that in 2012 about 319 600 new cases were reported globally, with around 76 100 deaths from the disease, and more women being affected in developed countries than developing countries.[1]

The International Federation of Gynaecology and Obstetrics (FIGO) adopted the surgical staging system in 1988 (revised in 2009), including pelvic and para-aortic lymphadenectomy. Surgical staging has assisted to better stratify prognostic groups. Lymphadenectomy for endometrial cancer is, however, still controversial. Some authors recommend routine lymphadenectomy in all endometrial cancer patients, but others deem this procedure unnecessary in low-risk patients.[2] The rate of lymph node metastases in endometrial cancer is below 15%, therefore it might be beneficial to have accurate means to predict the risk of metastases risk preoperatively.[3] Preoperative assessment of lymph node involvement is a critical step to determine the extent of surgery and prognosis, because lymph node metastasis is known to be a poor prognostic indicator. Other factors that also have a strong correlation with lymph node metastases are grade and myometrial invasion.[4,5]

Preoperative assessment of lymph node involvement is crucial to determine the need to extend surgery in patients with endometrial cancer and could individualise treatment plans. Since the discovery in 1981 of CA-125 as a circulating antigen in patients with epithelial ovarian cancer, this tumour marker has been widely used clinically for patients with endometrial cancer. High CA-125 levels are also strongly correlated with late stage of disease and lymph node metastasis.[6] The advantage of pre-operative determination of CA-125 in patient management is determining the risk of advanced disease and individualising the treatment plan for the patient. CA-125 level appears to be a better predictor of disease and, although it is still controversial,[4] many authors suggest it should be included as part of the preoperative workup for all patients with endometrial cancer.[7] This study aimed to evaluate the possibility of using CA-125 levels preoperatively to predict lymph node metastases in endometrial cancer patients, the need to perform lymphadenectomy in the surgical staging and the appropriate CA-125 cut-off point in our population and setting.

Methods

A retrospective audit was conducted for the period January 1, 2012 until January 1, 2017 at the Gynaecological Oncology Unit at the Steve Biko Academic Hospital, University of Pretoria. All patients with histologically confirmed endometrial carcinoma, underwent surgical staging and who had test results of preoperative CA-125 levels were included in the study. Patients who had previously received treatment in the form of radiation and/or chemo-radiation, as well as patients with pelvic endometriosis or primary ovarian tumours, were excluded. In all, 273 patient records were evaluated according to inclusion criteria and completeness of data, 179 patients were excluded due to incomplete records and a total of 58 patients were included in this study. Patient records were reviewed to obtain information on age, FIGO stage (performed according to the FIGO 2009

criteria), histology type and grade, depth of invasion, lymph node, ovarian and cervical involvement as well as preoperative serum CA-125 values.

Statistical analysis was performed using the descriptive statistics in the form of means and standard deviations in the case of continuous normally distributed data and medians and ranges where this was not the case. In the case of categorical data frequencies and percentages were used. The Spearman correlation was used to evaluate the association of preoperative CA-125 levels with a variety of factors. The receiver operating characteristic (ROC) curve was used to show the relationship between the sensitivity and 1-specificity (false positive) at different cut-off values of serum CA-125 levels for lymph node metastases. Chi-square tests were used to compare levels of CA-125 above and below 20 and early and late stage and lymph node metastases. This was repeated using CA-125 levels above and below 35 IU/ml. The analysis was conducted using SPSS software (Version 18.0; SPSS Inc, Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (Ref no. 45/2018).

Results
Fifty-eight participants who met the inclusion criteria were included in the study. The mean age of the study cohort was 63.0 years (standard deviation [SD] 8.80; range 41–84 years).

All patients underwent surgical staging, total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic and/or para-aortic lymph node (LN) dissection. Fifty-three (94.6%) patients had postmenopausal bleeding. The median value of lymph nodes that was removed was 10 lymph nodes (SD 8.96; range 1–46 nodes), and the median value of preoperative CA-125 serum was 21 IU/ml (SD 85.39; range 3–400 IU/ml).

Histological results showed 31 (53.4%) patients with endometrial carcinoma type I (endometrioid type) and 34 (58.6%) patients with grade III tumours. Myometrial invasion of more than 50% was present in 35 (60.3%) patients and lymph node metastasis in 19 (32.8%) patients. Nine (15.5%) patients had ovarian involvement; 15 (25.9%) women had parametrial involvement.

There was no significant correlation of CA-125 with histopathological type ($p = 0.257$), but there was a significant correlation with grade ($p < 0.05$), advanced stage ($p < 0.001$) and depth of invasion ($p < 0.001$). In extra-uterine metastasis, CA-125 values were found to be statistically significant different for lymph node metastasis ($p < 0.001$), cervical ($p < 0.05$) and ovarian involvement ($p < 0.05$). Table 1 shows the clinical characteristics of the study group. P-values were obtained using the Spearman correlation test.

ROC curves were used to determine the best cut-off value of preoperative serum CA-125 levels for prediction of lymph node metastases (Figure 1). In the current study, the best cut-off value was determined to be 20 IU/ml, and the sensitivity and

Table 1: Clinical characteristics of the study group

| Variable	n (%)	Median CA-125 level (IU/ml)	Mean ± SD CA-125 level (IU/ml)	p-value
FIGO stage:				
Stage I	24 (41.4)	14	64.29 ± 142.62	0.000
Stage II	9 (15.5)	27	58.85 ± 67.16	
Stage III	21 (36.2)	34	69.66 ± 96.16	
Stage IV	4 (6.9)	264.5	706.00 ± 1445.29	
Histology type:				
Endometrioid	31 (53.4)	15	38.06 ± 55.06	0.257
Clear cell	2 (3.1)	23.5	23.50 ± 3.54	
Serous	20 (34.5)	29.5	87.30 ± 123.41	
Carcinosarcoma	4 (6.9)	42.5	41.25 ± 22.27	
Mucinous	1 (1.7)	19	19	
Histology grade:				
Grade I	9 (15.5)	13	16.11 ± 9.45	0.031
Grade II	15 (25.9)	14	35.20 ± 34.61	
Grade III	34 (58.6)	29	73.06 ± 105.53	
Lymph node involvement:				
Negative	39 (67.2)	13	24.38 ± 23.97	< 0.0001
Positive	19 (32.8)	47	116.11 ± 126.11	
Depth of invasion:				
MI < 50%	23 (39.7)	12	18.43 ± 21.38	< 0.0001
MI >50%	35 (60.3)	35	78.09 ± 102.35	
Ovarian involvement:				
Negative	49 (84.5)	15	40,98 ± 64,68	0.037
Positive	9 (15.5)	65	127.67 ± 140.39	
Cervical involvement:				
Negative	34 (58.6)	14	30.15 ± 42.82	0.004
Positive	24 (41.4)	34.5	88.83 ± 115.46	
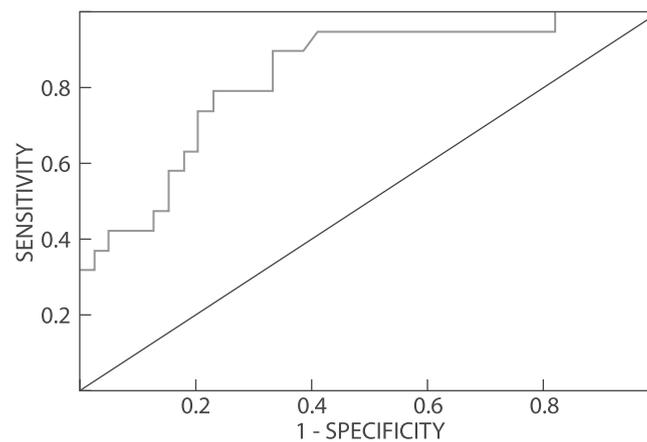
Figure 1: ROC curve drawn at different cut-off values of preoperative CA-125 levels for lymph node metastasis (area under the curve (AUC) = 0.831)

specificity for detecting lymph node metastases were found to be 89.5% and 67.0% respectively. The sensitivity and specificity of a conventional CA-125 cut-off level of 35 IU/ml in our population were 63.0% and 79.5% respectively.

When patients were classified into an early stage (FIGO stage 1) and a later stage (FIGO stages II–IV) category, 24 (41.4%) women were in the early-stage category, and 34 (58.6%) women in the later stage category. Two cut-off values for serum CA-125 were considered: 20 IU/ml and 35 IU/ml. Table 2 shows the distribution of the early stage versus later stage category using these two cut-off values. There was a significant difference between early and later stage patients when considering both the serum CA-125 cut-off points of 20 IU/ml and 35 IU/ml ($p <$ 0.001), but the sensitivity and specificity is higher at the cut-off point of 20 IU/ml.

When patients were classified according to lymph node metastasis, 19 (32.8%) showed lymph node involvement. Table 3 shows the distribution of lymph node involvement when considering the two cut-off serum CA-125 values of 20 IU/ml and 35 IU/ml. The best cut-off value for assessment of lymph node metastasis in our population was determined to be 20 IU/ml.

Discussion

Results of the current study demonstrated that the sensitivity of CA-125 was relatively high, as shown in Figure 1. Serum CA-125 levels had a very strong correlation and might be useful for prediction of advanced stage, lymph node metastasis and depth of myometrial invasion. Furthermore, the findings indicated that a cut-off value of 20 IU/ml has a sensitivity of 89.5% and a specificity of 67.0%. This result is lower than the conventional cut-off point of 35 IU/ml and that used in some previous studies: Jiang *et al.* suggested a cut-off point of 25 IU/ml for preoperative CA-125 serum levels,[8] while Choi *et al.* suggested a cut-off point of 30 IU/ml for extra-uterine disease and 50 IU/ml for lymph node metastasis, respectively.[9] Hsieh *et al.* demonstrated that elevated CA-125 levels preoperatively had significant correlation with lymph node metastasis, advanced stage, depth of invasion and cervical invasion with a cut-off point of 40 IU/ml, and can be considered for full pelvic lymphadenectomy.[10]

Other studies that showed a lower cut-off point of 20 IU/ml include the study by Dotters *et al.*, with the same cut-off point, who also claimed that CA-125 levels are useful to identify endometrial cancer patients in need of a lymphadenectomy.[11] Sood *et al.* suggested that extra-uterine disease would be less than

Table 2: Serum CA-125 value for FIGO stages according to cut-off value of 20 IU/ml and 35 IU/ml

FIGO stage	CA-125 < 20 IU/ml *n* (%)	CA-125 > 20 IU/ml *n* (%)	Total *n* (%)	*p*-value
Early stage (FIGO I)	18 (75.0)	6 (25.0)	24 (41.4)	0.001
Later stage (FIGO II-IV)	10 (29.4)	24 (70.6)	34 (58.6)	
FIGO stage	**CA-125 < 35 IU/ml** *n* (%)	**CA-125 > 35 IU/ml** *n* (%)	**Total** *n* (%)	***p*-value**
Early stage (FIGO I)	20 (83.3)	4 (16.7)	24 (41.4)	0.001
Later stage (FIGO II-IV)	17 (50.0)	17 (50.0)	34 (58.6)	

Table 3: Serum CA-125 value for lymph node involvement according to cut-off value of 20 IU/ml and 35 IU/ml

Lymph node involvement	CA-125 < 20 IU/ml *n* (%)	CA-125 > 20 IU/ml *n* (%)	Total *n* (%)	*p*-value
Negative	26 (66.7)	13 (33.3)	39 (67.2)	< 0.0001
Positive	2 (10.5)	17 (89.5)	19 (32.8)	
Lymph node involvement	**CA-125 < 35 IU/ml** n (%)	**CA-125 > 35 IU/ml** n (%)	**Total** n (%)	p-*value*
Negative	31 (79.5)	8 (20.5)	39 (67.2)	< 0.0001
Positive	6 (31.6)	13 (68.4)	19 (32.8)	

3% in patients with endometrial cancer with a cut-off point ≤ 20 IU/ml.[12] The normal CA-125 level in postmenopausal women is < 15 IU/ml, which is significantly lower than in premenopausal women. A study by Jiang *et al*. demonstrated that CA-125 levels are also related to age and menopause;[8] Chao *et al*. even proposed the use of an age-adjusted cut-off for preoperative CA-125 levels to improve lymph node metastases prediction.[13]

We acknowledge the fact that 93.1% of our study population were in the postmenopausal stage, which might be the reason for the lower cut-off point. Our results compared favourably to a study of postmenopausal women with endometrial cancer, also suggesting a CA-125 cut-off point of 20 IU/ml.[14] This value might be useful as cut-off point in postmenopausal patients with endometrial cancer. A CA-125 cut-off point of 20 IU/ml would enable the detection of 89.5% of patients with lymph node metastasis. The specificity of 67% is, however, low in our study, which means that we would have a false-positive rate of 33%.

As the first serum tumour marker test for epithelial ovarian cancer, CA-125 should be a good predictor for adnexal involvement in endometrial cancer. Our study indeed showed significant correlation between elevated CA-125 levels and adnexal involvement, as also demonstrated by Kim *et al*.[15] This result might be helpful in preoperative fertility-sparing consultation with young women with endometrial cancer.

In our study, preoperative CA-125 levels higher than 20 IU/ml were associated with lymph node metastasis and therefore advanced stage. In low-resource settings such as ours, CA-125 may be helpful to determine which patients will benefit from referral to oncologic gynaecology centres for complete lymphadenectomy.

There are limitations to our study. First, this was a retrospective study where intraoperative and postoperative management of patients with elevated serum CA-125 levels were not different from those with normal values. Second, there was a selection bias in that almost 75% of 237 patients were excluded due to unavailability of preoperative CA-125 levels and other missing data. In addition, this was a single-centre study, and larger prospective multi-centre studies would be needed to confirm results and to provide treatment recommendations for patients with endometrial cancer using preoperative CA-125 levels as predictive value.

To our knowledge, this was the first retrospective study of its kind to demonstrate a cut-off point for preoperative CA-125 levels in endometrial cancer in South African patients and might be a good source for future studies in similar settings.

Conclusions
Higher Ca-125 levels in this group of women with endometrial cancer appear to be associated with lymph node metastases, while we found CA-125 levels of 20 IU/ml or more to be predictive. Our findings suggest that, among similar populations, CA-125 could be done preoperatively and could be used to determine the need for node dissection. Since our findings are from a small retrospective cohort, this should be validated in a prospective study on early stage disease.

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