Correlation Between Preoperative Serum CA 125 and Surgicopathologic Prognostic Factors in Endometrial Cancer

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Abstract

Objective: This prospective study was conducted to determine the correlation between preoperative serum CA 125 and the presence of surgicopathologic prognostic factors in endometrial cancer. It also aimed to determine the CA 125 value which best predicted the prognostic factors to which it was significantly correlated.

Methods: Patients with endometrioid endometrial cancer eligible for primary surgery were included. CA 125 determination using a chemiluminescent enzyme immunoassay (CLEIA) was done before surgery. Patients underwent laparotomy, peritoneal fluid cytology, extrafascial/radical hysterectomy, bilateral salpingooophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling. Specimens were examined for tumor differentiation, lymphovascular space invasion, myometrial invasion, cervical, adnexal and vaginal involvement, pelvic and para-aortic lymph node metastases and for the presence of tumor cells in the peritoneal fluid. Correlation between CA 125 and the prognostic factors was analyzed using Pearson r correlation test. A receiver operating characteristic curve (ROC) was constructed to determine the CA 125 cutoff value.

Results: Ninety patients were included in the analysis. Preoperative serum CA 125 was significantly correlated with deep myometrial invasion (\( \sigma = 0.24, p = 0.02 \)), adnexal metastasis (\( \sigma = 0.26, p = 0.01 \)) and pelvic (\( \sigma = 0.31, p < 0.01 \)) and para-aortic lymph node involvement (\( \sigma = 0.43, p < 0.01 \)). It was also significantly correlated with the presence of extratubine disease (\( \sigma = 0.26, p = 0.01 \)). A value of 55 U/mL can predict extratubine spread with sensitivity of 53.85%, specificity of 84.38% and accuracy of 75.56%. Using this cutoff, the odds of a positive test is 3.44 and the odd of a negative test is 0.54.

Conclusion: Preoperative serum CA 125 has a statistically significant correlation with deep myometrial invasion, adnexal metastasis, pelvic and para-aortic lymph node involvement and extratuberine disease, at a cutoff value of 55 U/mL. CA 125 determination should be routinely performed as part of the preoperative work-up for patients with endometrioid endometrial cancer.

Keywords: Serum CA 125; Endometrial cancer; Preoperative assessment; Surgico-pathologic prognostic factors

Introduction

Serum CA 125 has been widely accepted and used in the follow-up of patients with epithelial ovarian carcinomas. In the 1980s, interest in its application in endometrial malignancies began to emerge, when Niloff et al. [1] noted elevated levels of this tumor marker in recurrent or disseminated disease. Numerous studies subsequently evolved, linking it with different prognostic factors, such as depth of myometrial invasion [2-6], stage [3-6], grade [2-4,6], lymphovascular space invasion [4], cervical involvement [3,5], adnexal involvement [7], positive cytology [3,5,6] and most notably, lymph node metastases [3-6,8-10]. Others demonstrated its role as an independent predictor of extratuberine disease, better than any of the surgicopathologic prognostic factors [2,4,11]. Trials exploring its use in the preoperative assessment [2,4] and post-treatment surveillance [3,12-14] of patients afflicted with the disease were also conducted. Some authors even recommended routine determination of serum CA 125 prior to surgery [2,4,5,10,11,15] to identify patients in whom standard systematic lymphadenectomy may be omitted [8,16,17] and in whom vaginal hysterectomy may be performed [6]. Corollary to these, studies on the cutoff level of this tumor marker that would be most predictive of disease and prognosis were suggested, with conflicting recommendations among various authors [2,4,7,10,14,16,17]. Although trials supporting its role in endometrial malignancies abound, its routine use has never been advocated due to contradictory results. This study was conducted to determine the correlation between preoperative serum CA 125 and the presence of surgicopathologic prognostic factors in endometrial cancer. Recommendations regarding routine preoperative determination, appropriate surgical approach and cutoff level will be made.

Materials and Methods

Patients with histologically confirmed endometrioid endometrial cancer who were medically fit to undergo surgery were included in the study. These patients must also have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2, no concomitant or previous malignant disease, did not receive previous radiotherapy or chemotherapy and with informed consent. Patients with uterine sarcoma, uterine papillary serous carcinoma (UPSC) and clear cell endometrial carcinoma were excluded from the analysis.

Blood was extracted for serum CA 125 determination two weeks prior to surgery. Samples were submitted to an Immunopathology Laboratory and processed using a chemiluminescent enzyme immunoassay (CLEIA).

Patients underwent exploratory laparotomy and complete surgical staging, which included peritoneal fluid cytology, extrafascial or radical hysterectomy, bilateral salpingooophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling. Specimens were examined for tumor differentiation, lymphovascular space invasion, myometrial invasion, cervical, adnexal and vaginal involvement, pelvic and para-aortic lymph node metastases and for the presence of tumor cells in the peritoneal fluid. Correlation between CA 125 and the prognostic factors was analyzed using Pearson r correlation test. A receiver operating characteristic curve (ROC) was constructed to determine the CA 125 cutoff value.

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lymph node dissection and para-aortic lymph node sampling. Those with clinical stage II endometrial cancer, documented by biopsy or curettage, underwent radical hysterectomy.

Tissue specimens submitted to the Pathology Laboratory were examined for surgicopathologic prognostic factors such as histologic type, tumor differentiation, lymphovascular space invasion, depth of myometrial invasion, cervical, adnexal and vaginal involvement, pelvic and para-aortic lymph node metastases and presence of tumor cells in the peritoneal fluid. Stage of disease was based on the final histopathologic reading.

Descriptive statistics (frequency observation and percentages) were used for the general description of the sociodemographic profile of patients and of the surgicopathologic prognostic factors. Pearson $r$ correlation test was used to evaluate the correlation between preoperative serum CA 125 and the different prognostic factors in endometrial cancer. A receiver operating characteristic curve (ROC) was used to determine the optimal cutoff value of preoperative CA 125 that would be most predictive of the prognostic factors to which it was shown to be correlated. Sensitivity, specificity, accuracy and likelihood ratios were calculated.

**Results**

Ninety patients diagnosed with endometrioid endometrial cancer underwent laparotomy and complete surgical staging. The mean age of patients is 50.9 years old. Thirteen patients (14.4%) were 40 years old or younger. Half of the population was postmenopausal. Nineteen percent was obese (Table 1).

The surgicopathologic prognostic factors are shown in Table 2. Majority of tumors were moderately differentiated and had no lymphovascular space invasion. Half of the cases had superficial myometrial invasion. Cervical involvement was found in 40%, majority of which infiltrated into the endocervical stroma. Only one-tenth of the tumors showed metastasis to the adnexal structures. Vaginal involvement was seen in only one patient. None of the peritoneal fluid was positive for malignant cells. One-fourth of the cases demonstrated pelvic lymph node involvement, while one-eighth showed metastasis to para-aortic nodes. Seventy-one percent had early stage disease. Some [21]. Concerns were raised, such that FIGO recommended a complete surgical staging procedure only for patients in whom certain subtypes, all of which were shown to correlate with the extent of the disease [20]. However, such parameters can be accurately determined only after exploration has been undertaken. It thus becomes necessary to provide a better estimate of the risk of extrauterine tumor spread and subsequently aid the planning of therapy. Preoperative identification of individuals who are most likely to have advanced stage disease and who will benefit from complete staging, will provide an opportunity to tailor surgical treatment individually [6].

A receiver operating characteristic curve (ROC) was constructed to depict the relationship between the sensitivity and specificity of CA 125 in predicting a stage III disease (Figure 1).

**Discussion**

Endometrial cancer ranks fourth as the most common cancer among females and seventh as the leading cause of death from malignancy in this population [18]. In the Philippines, it is the ninth leading site of cancer among women, with an incidence of 3.2% [19]. Ever since the FIGO (International Federation of Gynecology and Obstetrics) system changed from clinical to surgical staging in 1988, management of endometrial cancer has been primarily surgical and consisted of extrafascial total hysterectomy, bilateral salpingooophorectomy, peritoneal fluid cytology and selective pelvic or para-aortic lymphadenectomy [20]. Routine performance of such an extended surgical procedure, however, has been criticized by some [21]. Concerns were raised, such that FIGO recommended a complete surgical staging procedure only for patients in whom certain prognostic factors can be identified. These include high grade tumors, full thickness myometrial invasion, grossly positive adnexae, grossly positive pelvic nodes, suspicious aortic or common iliac nodes and tumors with clear cell, papillary serous or carcinosarcoma histologic subtypes, all of which were shown to correlate with the extent of the disease [20]. However, such parameters can be accurately determined only after exploration has been undertaken. It thus becomes necessary that adequate preoperative work-up be done in order to provide a better estimate of the risk of extraterine tumor spread and subsequently aid in the planning of therapy. Preoperative identification of individuals who are most likely to have advanced stage disease and who will benefit from complete staging, will provide an opportunity to tailor surgical treatment individually [6].
Although various imaging modalities (ultrasonography, CT scan, MRI) may be used, these preoperative tools are not universally available, have prohibitive costs and have limited sensitivity and specificity in predicting the true extent of disease and the need for an extended surgical staging procedure. In the quest for other cost-effective, more reliable tests, several authors have explored the use of serum CA 125
in the preoperative setting as a marker of extent of disease and tumor spread.

CA 125 is a tumor antigen expressed by structures derived from the coelomic epithelium and from tubal, endometrial and endocervical epithelium [1,22]. It may be elevated in benign conditions and physiological states such as endometriosis, pregnancy and menstruation [22]. In this study, analysis has shown that CA 125 values were not affected by the presence of associated conditions such as endometriosis, adenomyosis or leiomyoma (Table 3). This tumor marker may also be elevated in gynecologic cancers and in malignancies of the pancreas, colon, breast and lungs [22]. In gynecology, it has been widely accepted and used to follow the clinical course of ovarian cancer, predict tumor response to chemotherapy and subsequently prognosticate survival [23-25].

In endometrial cancer, meanwhile, investigations on the clinical application and significance of this tumor marker both in the primary and recurrent setting of the disease have yet to be clearly defined. In the current study, analysis of the correlation of a preoperatively determined serum CA 125 level demonstrated a significant association with the presence of adnexal metastases and pelvic and para-aortic lymph node involvement (Table 3). This was further validated by the significant correlation between elevated CA 125 and the presence of extraterine disease. A significant direct association was also noted with depth of myometrial invasion. Although deep myometrial invasion alone is equivalent to a stage IB endometrial malignancy, further analysis revealed that among those with tumors infiltrating deep into the myometrium, majority had either adnexal, vaginal, or retroperitoneal lymph node metastases as well. The significant correlation between CA 125 and depth of myometrial invasion could thus be attributed to the presence of the other prognostic factors that were indicative of extraterine spread of disease. Therefore, the relationship between this tumor antigen and a stage III malignancy is still upheld. Possible explanation to this association between increasing CA 125 levels and advancing stage has been postulated. Some authors theorized that the intrauterine location of the tumor could limit access of the tumor antigen into the circulation such that CA 125 levels remain low in the early stage of the disease. It becomes elevated only when the tumor invades the blood and lymphatic channels, becomes intraperitoneal, or is associated with bulky nodal metastasis [5,16].

Consistent with the findings of the present study are those of Jhang et al. [4] who demonstrated that elevated CA 125 levels is a significant independent predictor of lymph node metastases and advanced stage. In another study, a multivariate analysis of clinicopathologic variables demonstrated that nodal metastases had the most significant effect on the elevation of preoperative CA 125. Patients with retroperitoneal lymph node involvement have a 7.7-fold higher risk of having CA 125 levels above 40 U/mL [5]. Todo et al. [8] suggested that serum CA 125 elevation is more useful than depth of myometrial invasion and histologic grade in predicting lymph node metastasis. Although the study by Dotters did not find any correlation between elevated preoperative CA 125 values and nodal metastases, the author however, found significant association with deep myometrial involvement, angiolymphatic invasion, cervical extension, grade 3 tumor, high-risk histologic type, large primary tumors (>6 cm), positive peritoneal

### Table 4: Sensitivity, Specificity, Accuracy and Likelihood Ratios of the prognostic factors at CA 125 cutoff value of 55 U/mL

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Likelihood ratio (+)</th>
<th>Likelihood ratio (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myometrial Invasion &gt; 50%</td>
<td>50.00</td>
<td>87.50</td>
<td>77.33</td>
<td>4.00</td>
<td>0.57</td>
</tr>
<tr>
<td>Adnexal Involvement</td>
<td>50.00</td>
<td>76.25</td>
<td>73.33</td>
<td>2.10</td>
<td>0.65</td>
</tr>
<tr>
<td>Pelvic Lymph Node Involvement</td>
<td>52.38</td>
<td>81.16</td>
<td>74.44</td>
<td>2.78</td>
<td>0.58</td>
</tr>
<tr>
<td>Para-aortic Lymph Node Involvement</td>
<td>72.73</td>
<td>79.75</td>
<td>78.89</td>
<td>3.59</td>
<td>0.34</td>
</tr>
<tr>
<td>Stage III Disease</td>
<td>53.85</td>
<td>84.38</td>
<td>75.56</td>
<td>3.44</td>
<td>0.54</td>
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**Figure 1:** Receiver-operating characteristic curve (ROC) of CA 125 values for Stage III Disease.
cytologic findings and extraterine disease, factors which strongly predicted the need for lymphadenectomy. Similarly, Sood et al. [6] established a significant correlation not only with lymph node involvement, but also with stage, grade, depth of myometrial invasion, positive cytology and reduced actuarial survival. The authors further noted that a preoperative CA 125 value above 65 U/mL was the most significant predictor of extraterine disease with a 6.5-fold higher risk.

Among the CA 125 levels obtained in this study, a cutoff value of 55 U/mL was determined to be the most appropriate level that is best predictive of the surgicopathologic prognostic factors to which it has been shown to be correlated. This cutoff level differs from those suggested in literature. Several cutoff values have been proposed: 20, 35, 37, 40, 70 U/mL [6,14,16,11,4,10], with varying levels of sensitivity and specificity. These variations in CA 125 absolute cutoff values may be attributed to the fact that in the present study, only endometrioid type histologies were included, with the intention of making the population as homogenous as possible. The inclusion of unfavorable histologic types in the other studies may have affected their results since the behavior of these non-endometrioid types parallels that of ovarian carcinoma and thus can influence the absolute value of the CA 125 test. However, this relationship could not be proven in the present study with a separate sub-analysis since only three cases of poor histologic types were gathered during the course of patient recruitment. Only the study by Kim et al. [7] reported on endometrioid endometrial cancer patients alone. In their retrospective review, the authors found that the different poor prognostic factors can be predicted using different CA 125 cutoff values, ranging from 18.0 to 40.8 U/mL, with adnexal involvement being predicted with an accuracy as high as 82.9%. Although these results parallel those obtained from the present study, the difference in the absolute CA 125 cutoff value may be due to a difference in the CA 125 assay used. This also holds true for the other previously mentioned studies, which used immunoradiometric assay [5,14], enzyme immunoassay [6] and microparticle enzyme immunoassay [16]. In contrast, a luminometric immunoassay was used in the present study due to its availability and lower cost. A comparison of these assays showed that although there is an overall tendency towards higher absolute values in the lower CA 125 value range in some assays, all were nevertheless linearly correlated with each other. Furthermore, no single CA 125 assay offers higher diagnostic accuracy or better discrimination, especially in the lower ranges (0-100 U/mL). The authors, however, emphasized that results from the different methods should not be interchanged during the course of monitoring disease progression in the same patient [26].

Among the gynecologic cancers, endometrial cancer is the most likely disease to be managed by a general gynecologist, especially if the disease seemed to be confined to the uterine corpus. A preoperative serum CA 125 determination will provide benefit in identifying patients in whom a full surgical staging procedure is indicated. A value greater than 55 U/mL could suggest the need for referral to a gynecologic oncologist. The benefit of the performance of lymphadenectomy in such cases need not be overemphasized, since the 5-year survival rates for clinically staged stage I disease have been found to be similar to patients with surgically staged stage III disease [27], suggesting that recurrences and deaths from the former are possibly secondary to undetected lymph node metastasis that would have upstaged a significant proportion of clinical stage I cases to surgical stage III disease had lymph nodes been examined systematically [15].

The information obtained from this investigation can also aid the gynecologic oncologist during preoperative counseling and in tailoring the appropriate treatment and surgical management. For patients whose disease is confined to the uterine corpus, with favorable histologic type and tumor differentiation as determined by curettage or biopsy and in whom preoperative serum CA 125 is below 55 U/mL, the option of a vaginal hysterectomy may be entertained. This alternative surgical approach is appropriate for obese patients who comprise 19% of our endometrial cancer population, in whom the abdominal route may be technically difficult. The only disadvantage with a vaginal hysterectomy is the inability to adequately assess the lymph nodes and other abdominopelvic organs intraoperatively. Therefore, the decision to perform hysterectomy by the vaginal route and omit complete lymphadenectomy should be made after taking into consideration all the other prognostic factors that are available preoperatively, including histologic type and tumor differentiation, as well as the results of imaging studies and serum CA 125 test.

In this analysis, 53 patients were assessed preoperatively as having disease confined to the corpus. Of these, endometrial biopsy or curettage identified 25 well-differentiated tumors and 20 moderately differentiated ones. Of the 25 clinically stage I grade 1 tumors, 4 patients had serum CA 125 values above 55 U/mL, all of whom had prognostic features that warranted full surgical staging (1 case each of stage IB and II disease and 2 cases with retroperitoneal lymph node involvement). None of the cases was thus overtreated. Two of the 21 patients who had CA 125 values below the cutoff level were upstaged on final histopathology (1 case to IIIC and another to II). Thus among well-differentiated tumors, taking preoperative serum CA 125 level into consideration would upstage 3 cases of apparent early stage disease. Only a single case of lymph node metastasis would have been missed. On the other hand, of the 20 clinically stage I grade 2 tumors, 5 patients had serum CA 125 values above 55 U/mL, all of whom also had pathologic factors that required a comprehensive surgical staging (2 cases with stage IB disease, 1 case of stage II and 2 cases of stage IIIC malignancy). Again, no overtreatment occurred. Of the 15 patients with CA 125 values below the cutoff level, 4 were upstaged as follows: 2 upstaged to II and 2 cases of IIIC, after histopathologic examination of the definitive specimens removed during full surgical staging. Thus, among moderately differentiated tumors, taking preoperative CA 125 levels into consideration would upstage 3 cases of apparent early stage tumors and will overlook 3 cases with extraterine disease, two of which had lymph node involvement. This overall failure to predict 3 cases of lymph node metastasis and 1 case of adnexal involvement in apparent early stage tumors can probably be secondary to the 16% [8] to 20% [20] inaccurate rate of tumor differentiation determined from an endometrial curettage sample compared to that taken from the hysterectomy specimen.

Alternatively, perhaps this inability to absolutely predict the presence of extraterine spread could be improved when depth of myometrial invasion determined by preoperative imaging studies is also considered. This is in congruence with the recommendation by Kim et al. [7] who noted that CA 125 levels alone were not enough to predict most of the prognostic factors, such that additional imaging studies are necessary. The most accurate means of assessing depth of myometrial invasion is through MRI [20]. Lee et al. [10] explored the feasibility of using these preoperative diagnostic data to identify the risk of lymph node metastasis in endometrial cancer. The authors developed a scoring system composed of histologic grade, CA 125 and MRI assessment of depth of myometrial invasion and extent of disease. Using this system, a group of patients who are at low risk for nodal metastasis can be identified. The authors concluded that such prediction model may be useful in the preoperative counseling of patients regarding the benefits and risks of lymphadenectomy, or in referring high-risk
patients to gynecologic oncologists for comprehensive surgical staging. However, the authors noted that one of the limitations of their study is its inapplicability in the low-resource setting because the prediction model used diagnostic information provided by the MR image. Such is the case in the Philippines where the routine use of MR scanning as part of preoperative work-up for all cases of endometrial cancer is too costly. What has been accepted in clinical practice is to use sonography to evaluate myometrial infiltration. A local study demonstrated that this imaging modality has a sensitivity of 82.61%, specificity of 71.83%, positive predictive value of 65.52% and negative predictive value of 86.44% in predicting deep myometrial invasion [28]. Unfortunately, the accuracy rate of these three modalities (tumor grade, serum CA 125, depth of myometrial invasion by ultrasonography) taken together in predicting extruterine spread of endometrial malignancy is beyond the scope of this investigation. Suffice it to say that with a CA 125 value below 55 U/mL, the option of performing vaginal hysterectomy for patients with disease confined to the uterine corpus, well- or moderately-differentiated tumors by curettage and superficial myometrial invasion by ultrasonography, deserves further consideration.

In conclusion, results of this investigation have shown that preoperative serum CA 125 has a statistically significant correlation with deep myometrial invasion, adnexal metastasis and pelvic and para-aortic lymph node involvement. A cutoff value of 55 U/mL can predict the presence of extruterine disease with a sensitivity of 53.85%, specificity of 84.38% and accuracy of 75.56%. Using this value, taken together with histologic type, tumor differentiation and depth of myometrial invasion, patients with preoperative serum CA 125 below the cutoff level may be considered for vaginal hysterectomy without the need for a complete lymphadenectomy. Alternatively, patients with CA 125 level greater than 55 U/mL necessitate referral to a gynecologic oncologist for preoperative counseling and appropriate surgical management. It is thus recommended that serum CA 125 determination be routinely performed as part of the preoperative work-up for patients with endometrioid endometrial cancer.

References