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Predictive value of Kanagawa cancer center scoring system for lymph node metastasis in patients with endometrial cancer and comparing it to Al-Hilli scoring system

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Abstract
Background: Lymph node metastasis (LNM) is an indicator of poor prognosis and requires adjuvant therapy in patient with endometrial cancer (EC). Lymphadenectomy is still the standard technique to assess the lymphatic spread of EC. However, the evaluation of the LNM preoperatively is an important factor in determining the outcome of patients with endometrial cancer. The Kanagawa Cancer Center (KCC) scoring system allows to identify patients risk of developing LNM based on tumor volume, myometrium invasion, histological type, and serumCA125 levels.
Objective: To determine the predictive value of Kanagawa Cancer Centre (KCC) scoring system for lymph node metastasis in patients with endometrial cancer and compare it with Alhilli scoring.
Patients and Methods: A prospective observational cross-sectional study carried out in the Department of Obstetrics and Gynecology / Baghdad Teaching Hospital, Baghdad, Iraq over a period of 20 months starting from December 2018 to August 2020. A total number of 52 patients with endometrial cancer were included. Preoperative assessment included histology and CA125.
Results*:* The cut point of KCC score was 2, so KCC > 2 is predictive for lymph node involvement. The sensitivity, specificity, positive predictive value, and negative predictive value of KCC for lymph node involvement was found to be 100%, 95.5%, 80%, and 100%, respectively, with an accuracy of 96.2%. Lymph node involvement was seen significantly in patients with positive CA125 level, grade 3, non-endometrioid type, myometrium invasion ≥ 50%, and higher tumor volume. Regarding Al-hilli scoring system, the sensitivity, specificity, positive predictive value and negative predictive value was 100%, 40.9%, 23.5%, 100% respectively, with an accuracy of 50%.
Conclusions: The KCC scoring system has a high accuracy for the prediction of lymph node involvement in patients with endometrial cancer with better accuracy than Al-hilli scoring.

Keywords: Kanagawa cancer centre scoring, endometrial cancer, CA125, Al-hilli scoring

Introduction
Adenocarcinoma of the endometrium (also known as endometrial cancer, or more broadly as uterine cancer or carcinoma of the uterine corpus) is currently considered the most common gynecologic cancer with an estimate of 60,050 new cases and 10,470 deaths per year in the United States [1].
The mean age of patients at the time of diagnosis is 63 years, with 90% of cases occurring in women older than 50 years. Only 20% of patients with endometrial cancer receive a diagnosis before menopause [2].
Endometrial cancer is generally classified into two types (2). Type I is the most common form, representing the majority of cases. Type I tumors are associated with unopposed estrogen stimulation and are known as endometrioid adenocarcinoma [3]. These tumors are generally low grade. Type II tumors are more likely to be high grade and of papillary serous or clear cell histologic type. They carry a poor prognosis and have a high risk of relapse and metastasis. Type II accounts for only 10% of endometrial cancers, but it is associated with 40% of related deaths [2, 3]. Familial tumors are commonly found in association with Lynch syndrome (hereditary nonpolyposis colorectal cancer). Genetic disease represents 10% of cases of endometrial cancer [3]. Endometrial hyperplasia represents a precursor lesion to endometrial cancer. Hyperplasia carries a 1% to 3% risk of progression to cancer. Atypical hyperplasia is associated with greater cancer risk than simple or complex hyperplasia; 30% to 40% of patients with atypical hyperplasia have concomitant adenocarcinoma [2].

Demographic Patterns

1. Age

The majority of women diagnosed with endometrial cancer are peri- or postmenopausal between the ages of 50 and 65 [4]. The average age at diagnosis is 61 [5]. However, the risk of developing endometrial cancer increases with advancing age. For example, a woman under the age of 40 has a 1 in 1423 risk of developing the disease, but a woman older than 70 has a 1 in 81 risk [6].

2. Race / ethnicity and geographic considerations

In the United States, white women are more likely to be diagnosed with endometrial cancer than African-American, Asian, or Hispanic women [4]. The age-adjusted incidence rate for white women is 24.8 per 100,000 women, whereas it is 20.9, 18.2, and 15.9 for African-American, Asian, and Hispanic women, respectively [5]. However, African-American women have a higher mortality rate than the other racial groups at 7.2 per 100,000 women, compared with 3.9 for white women, 2.5 for Asian women, and 3.0 for Hispanic women [5]. In general, African-American women are more likely to present with regional or distant metastasis, have high-risk tumor types, have less access to care, and have more medical co morbidities than other racial groups [4, 6, 7].

When incidence data from other parts of the world for endometrial cancer are studied, a number of observations can be made [8]. In general, the incidence is highest in developed countries. For example, the incidence of endometrial cancer is much higher in North America, Australia, and Europe than in Central and South America, Asia, and Africa [4, 9, 10].

Interestingly, when one compares among various regions within racial groups, there are differences noted in incidence rates. For example, studies have shown that the rates of endometrial cancer in African-American and Asian women living in the United States are higher than in women living in Africa or Asia [4]. Additionally, there are data to suggest that Chinese and Japanese immigrants to the United States have a higher risk of endometrial cancer than women who remain in China and Japan [10]. This suggests that environmental factors play an important role in the development of endometrial cancer.

Other variables that may explain regional variations in incidence rates include registration deficiencies as well as differences in risk factors, such as obesity rates, among populations [4, 7]. In Iraq the incidence rate of endometrial cancer was 2.31 per 100,000 women [11].

Aim of Study

To determine the predictive value of Kanagawa Cancer Centre (KCC) scoring system for lymph node metastasis in patients with endometrial cancer and compare it with Alhilli scoring.

Patients and Methods

Study design and setting

This is a prospective observational cross-sectional study, which was carried out in the Department of Obstetrics and Gynecology / Baghdad Teaching Hospital, Baghdad, Iraq. This study was conducted over a period of 20 months starting from December 2018 to August 2020.

Patients

Fifty-two patients with proved endometrial cancer based on preoperative endometrial tissue examination who were admitted to our center during the study period and underwent the initial surgery. (Total abdominal hysterectomy, bilateral Salpingo-oophorectomy and pelvic lymph node dissection) were included in this study.

Exclusion criteria

- Patients with endometrial cancer stage IV.
- Patients with coexisting ovarian cancer.
- Comorbidities making the lymphadenectomy improper. (morbid obesity, intra operative bleeding, etc)

Method

Pre-operative a sample of 3 cc of blood was collected from each patient and sent to the laboratory to measure serum CA-125 using Abbott™ ARCHITECT™ CA 125 II Analyzers

The assay is a chemiluminescent micropartcle immunoassay (CMIA) for the quantitative determination of OC 125 defined antigen in human serum and plasma on the ARCHITECT system.

Patients stratification

1. Alhilli stratification

All patients were evaluated intraoperatively using Alhilli stratification based on the tumor diameter (measured intra op.) and the Histological grade. Patient stratified into (Low, Intermediate and High) risk for Lymph node metastasis.

2. KCC scoring system

All the patients were evaluated intraoperatively using the KCC scoring system. (Table 1). Four criteria each assigned one score, were used: (1) tumor volume > 6 cm^3 (calculated based on intraoperative visual findings as the product of the maximum longitudinal diameter, the maximum anteroposterior diameter (thickness), and the maximum horizontal diameter.), (2) myometrial invasion above 50% (by intraoperative visual examination), (3) histological type other than G1 endometrioid adenocarcinoma on preoperative endometrial tissue examination, and (4) serum CA125 level higher than 70 U/ml for premenopausal and 25 U/ml for menopausal women.

Table 1: Four criteria each assigned one score, were used

Criteria	Parameter	Score
Tumor volume	≥6 mL	1
Myometrial invasion	≥50%	1
Preoprative histological subtype	Other than G1 endometrioid adenocarcinoma: ■ G2/G3 endometrioid adenocarcinoma ■ Serous adenocarcinoma ■ Clear cell adenocarcinoma ■ Carcinosarcoma, etc	1
Preoperative serum CA 125	>70 U/mL (for premenopause) >25U/mL(for postmenopause)	1

All the patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) along with pelvic lymphadenectomy (PLX) under general anesthesia. The resected lymph nodes were sent for histopathological examination. The

two scoring system were compared with the histopathology results, and the accuracy of the LNM prediction was evaluated accordingly.

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables accordingly. Chi square test was used to assess the association between lymph node involvement and certain information, while fisher exact test was used instead when the expected frequency was less than 5. Receiver operating characteristic (ROC) curve analysis was used for prediction of KCC score as predictor of lymph node involvement. A level of P – value less than 0.05 was considered significant.

Results

Clinical information

Table 2 shows the distribution of study patients by clinical information. In this study, the majority of study patients were menopause (80.8%).

Regarding carcinoma, the most common type was endometrioid (84.6%), 57.7% of patients were in grade 1 and 69.2% were in stage IA. CA125 level was high in 15.4% of them.

More than three quarters of patients showed myometrium invasion < 50% (76.9%).

Table 2: Distribution of study patients by clinical information

Variable	No. (n= 52)	Percentage (%)
Menopause		
Yes	42	80.8
No	10	19.2
CA 125 Level		
High	8	15.4
Normal	44	84.6
Type of carcinoma		
Endometrioid	44	84.6
Non endometrioid	8	15.4
Grade of carcinoma		
1	30	57.7
2	14	26.9
3	8	15.4
Stage of carcinoma		
IA	36	69.2
IB	4	7.7
II	2	3.8
IIIA	2	3.8
IIIC	8	15.4
Myometrium invasion		
< 50%	40	76.9
≥ 50%	12	23.1

Kanagawa Cancer Center (KCC) scoring system

Tables 3 and 4 show the distribution and comparison in KCC Scoring System by lymph node involvement. Mean of KCC scoring system was significantly higher in patients with lymph node involvement than that in those without lymph node involvement (3.0 versus 0.7, P= 0.001).

Table 3: Distribution of study patients by KCC score system

KCC Score	No. (n= 52)	Percentage (%)
0	18	34.6
1	20	38.5
2	4	7.7
3	10	19.2
4	0	0

Table 4: Comparison in KCC Scoring System by lymph node involvement

KCC Scoring System	Lymph node Involvement		P - Value
	Yes Mean ± SD	No Mean ± SD	
	3.0 ± 0	0.77 ± 0.8	0.001

Receiver operating characteristic (ROC) curve analysis was constructed for KCC score as predictor for lymph node involvement. As shown in tables (5), the cut point of KCC score was 2, so KCC > 2 is predictive for lymph node involvement. KCC score was 100% sensitive, 95.5% specific, and 96.2% accurate as a marker for prediction of lymph node involvement.

Table 5: Diagnostic accuracy for marker of lymph node involvement

KCC score	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	2	100%	95.5%	80%	100%	96.2%

Overall, eight patients (15.4%) tested positive for pelvic lymph node involvement. of the 10 patients who were predicted to have lymph node involvement 8 had lymph node involvement in pathology examination. of the 42 patients who were predicted not to have lymph node involvement none had lymph node involvement (table 6).

Table 6: Distribution of KCC score by lymph node involvement

KCC Score	LN involvement		
	Yes	No	Total
0-1-2	0	42	42
3-4	8	2	10
Total	8	44	52

Al-hilli Scoring System

The association between Al-hilli Scoring System and lymph node involvement is shown in table (7). We noticed that half of patients with high Al-hilli score had lymph node involvement with a significant association (P= 0.001) between Al-hilli Scoring System and lymph node involvement.

Table 7: Association between Al-hilli Scoring System and lymph node involvement

Al-hilli Scoring System	Lymph node Involvement		Total (%) n= 52	P - Value
	Yes (%) n= 8	No (%) n= 44		
Low	0 (0)	18 (100.0)	18 (34.6)	**0.001**
Intermediate	2 (9.1)	20 (90.9)	22 (42.3)	
High	6 (50.0)	6 (50.0)	12 (23.1)	

Table 8 shows the sensitivity, specificity, and accuracy of Al-hilli scoring system.
The sensitivity = 100%, specificity = 40.9% and accuracy of Al-hilli scoring system was 50%.
Positive predictive value was 23.5% while negative predictive value was 100%.

Table 8: Sensitivity, specificity, and accuracy of Al-hilli Scoring System

Al-hilli Scoring System	LN involvement		
	Yes	No	Total
High / Intermediate	8	26	34
Low	0	18	18
Total	8	44	52

Table 9 shows the association between lymph node involvement and clinical information. In this study, the highest prevalence of lymph node involvement was seen significantly in patients with high CA125 level (50%, P= 0.003), grade 3 (50%, P= 0.001), non-endometrioid type (50%, P= 0.003), myometrium invasion ≥ 50% (66.7%, P= 0.001), volume more than six cm^3 (33.3%, P= 0.001), and diameter > 2 cm (28.6%, P= 0.001).
No statistically significant associations (P ≥ 0.05) between lymph node involvement and both of age and menopause.

Table 9: Association between lymph node involvement and clinical information

Variable	Lymph node Involvement		Total (%) n= 52	P - Value
	Yes (%) n= 8	No (%) n= 44		
Age (Year)				
< 50	2 (33.3)	4 (66.7)	6 (11.5)	0.414
50 – 59	2 (11.1)	16 (88.9)	18 (34.6)	
≥ 60	4 (14.3)	24 (85.7)	28 (53.8)	
Menopause				
Yes	6 (14.3)	36 (85.7)	42 (80.8)	0.653
No	2 (20.0)	8 (80.0)	10 (19.2)	
CA125 Level				
High	4 (50.0)	4 (50.0)	8 (15.4)	0.003
Normal	4 (9.1)	40 (90.9)	44 (84.6)	
Grade				
1	0 (0)	30 (100.0)	30 (57.7)	0.001
2	4 (28.6)	10 (71.4)	14 (26.9)	
3	4 (50.0)	4 (50.0)	8 (15.4)	
Type of carcinoma				
Endometrioid	4 (9.1)	40 (90.9)	44 (84.6)	0.003
Non endometrioid	4 (50.0)	4 (50.0)	8 (15.4)	
Myometrium Invasion				
< 50%	0 (0)	40 (100.0)	40 (76.9)	0.001
≥ 50%	8 (66.7)	4 (33.3)	12 (23.1)	
Volume of tumor (cm^3)				
≤ 6	0 (0)	28 (100.0)	28 (53.8)	0.001
> 6	8 (33.3)	16 (66.7)	24 (46.2)	

The comparison in diameter of tumor by lymph node involvement is shown in table (10). Mean of diameter was significantly higher in patients with lymph node involvement than that in those without lymph node involvement (5.25 versus 2.75 cm, P= 0.002).

Table 10: Comparison in diameter of tumor by lymph node involvement

Diameter (cm)	Lymph node Involvement		P - Value
	Yes Mean ± SD	No Mean ± SD	
	5.25 ± 1.6	2.75 ± 2.0	0.002

Discussion

In the current study the mean age of the patient was 59.76 years and the highest proportion of study patients was aged ≥ 60 years. This is in agreement with what was mentioned by Howlader N., *et al* as the majority of women diagnosed with endometrial cancer are peri- or postmenopausal between the ages of 50 and 65 years and the average age at diagnosis is 61 years [5].

In the current study, premenopaused patients represent 19.2%. This is in agreement with Sorosky JI *et al* who mentioned that 20% of patients with endometrial cancer are premenopausal [2].
The majorities of our patients were in stage IA and IB (76.9%) This is in agreement with Yang B *et al*. [12] when both of stage IA and IB is found in (75.4%) of the studied group.
In our study, age showed no statistical significance to predict lymph node metastasis this is in agreement with Joo-Hyuk Son *et al* [13].
In our study patients with Grade 1 tumor and <50% myometrial invasion (MI) had no lymph node involvement, while half of the patients with Grade 3 tumor had lymph node involvement and 66.7% of patients with ≥ 50% myometrial invasion had lymph node involvement. This goes in agreement with Wakayama *et al* who mentioned that lymphatic and venous invasion were significantly more likely to present in advanced cancer stage, G3 tumor, and deep myometrium invasion. Lymphatic vessel invasion was significantly correlated with regional LNM. They reported lymphatic invasion as an independent prognostic factor along with distant metastasis [14].

The finding of a significant association between MI and LNM in our study is in concordance with what Vargas R, *et al* demonstrates in their study [15]. The reliability of measuring of MI intraoperatively using intraoperative gross examination or frozen section has been reported and show high sensitivity and specificity for both methods [16].

Mean of diameter was significantly higher in patients with lymph node involvement than that in those without lymph node involvement (5.25 ± 1.6 cm versus 2.75 ± 2.0 cm, P= 0.002). Lurain *et al*. [17]. showed a decrease in the risk of lymph node metastases and an increase of survival in tumors less than 2 cm. This is also mentioned by Milam MR *et al* [18]. In our study, the highest prevalence of lymph node involvement was seen significantly in patients with grade 3 (50%, P= 0.001), non-endometrioid type (50%, P= 0.003), and myometrium invasion ≥ 50% (66.7%, P= 0.001). This goes with what it is reported by Mariani *et al*.as patients with G1/G2 endometrioid adenocarcinoma, less than 50% of myometrial invasion, and tumor size less than two cm have low LNM risk [19].

In our study, we found a significant association between tumor volume more than 6 cm^3 and lymph node involvement (33.3%, P= 0.001). This cut off value used by KCC is more stringent than what was described by Mitamura *et al* [20] witch was 36 cm^3.

It is well known that an elevated CA-125 levels are associated with lymph node metastasis [21, 22]. In our study, the highest prevalence of lymph node involvement was seen significantly in patients with positive CA 125 level (50%, P= 0.003), patient was considered to have positive CA125 level if it was > 70 IU/ml in a premenopaused woman and > 25 IU/ml in a menopaused woman. That was based on previous studies by Nakayama *et al*. performed in the KCC [1, 24].

Alhilli *et al*. [23] introduced risk stratification based on tumor diameter, histological type and grade. Low risk patients had a very low risk of lymphatic dissemination or recurrence (<1%). Intermediate- and high-risk patients had 17% risk of lymph node metastasis and recurrence. In our study we noticed that half of patients with high Al-hilli score had lymph node involvement with a significant association (P= 0.001) between Al-hilli Scoring System and lymph node involvement. The sensitivity was 100%, the specificity was 40.9% and accuracy of Al-hilli scoring system was 50%. Positive predictive value was 23.5% while negative predictive value was 100%.

Recently, Imai *et al* [24] did a retrospective study of 653 patients with endometrial carcinoma by reviewing their medical records they classified them based on the KCC score and found that there was no difference in survival between patients with KCC score 0 whether they were treated with lymphadenectomy or not. Also they found that the KCC score system was more accurate than myometrial invasion alone in the prediction of LNM.

In a previous study, Mitamura *et al* [20] have demonstrated that lymphadenctomy can be omitted for low-risk endometrial cancer based on preoperative assessments using a scoring system similar to those of the KCC tumor volume < 36 cm^3, G1 or G2 endometrioid adenocarcinoma, CA125 levels less than 28 and 70 U/ml for patients aged >50 and ≤50 years, respectively, and no myometrial invasion. As a result, they have reported a low recurrence rate (1.8%) and 100% five-year survival rate.

The difference between our study and these two studies is that we used the histopathological examination of the lymph nodes to determine the accuracy of the KCC scoring system and their studies were retrospective while our study is prospective one.

In our study, we demonstrate that lymph node involvement was associated with higher KCC score (P= 0.001). The (ROC) curve showed a cutoff value of the KCC score of 2, so KCC > 2 is predictive for lymph node involvement. KCC score was 100% sensitive, 95.5% specific, the positive predictive value was 80%, negative predictive value was 100% and 96.2% accurate as a marker for prediction of lymph node involvement.

While, Momtahan *et al* [26] demonstrate that All the patients who had lymph node involvement had KCC higher than 1 with sensitivity, specificity, positive predictive value and negative predictive value of 35.3%, 100%, 100%, and 64% respectively. They also demonstrate that the KCC scoring system has a moderate accuracy for prediction of lymph node involvement. This could be due to the difference in sample size between the two studies. 52 Vs 94 and a different cutoff value 2 Vs 1.

To the best of our knowledge this is the first study to determine the accuracy of KCC scoring system in the prediction of lymph node involvement in Iraqi patients with endometrial cancer and comparing it to Alhilli stratification.

Conclusion

Kanagawa Cancer Center (KCC) scoring system could be used to predict lymph node metastasis in patients with endometrial cancer with better accuracy than Al-hilli scoring.

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