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การใช้สารบ่งชี้ค่ามะเร็งรังไข่ในเลือดเพื่อแยกกลุ่มเนื้องอกรังไข่แบบเยื่อเมือกชนิดต่างๆ

The Use of CEA CA12-5 and CA19-9 as Serum Tumor Markers to Differentiate Subtypes of Mucinous Ovarian Tumors

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บทคัดย่อ

หลักการและเหตุผล : เพื่อประเมินประสิทธิภาพในการจำแนกระหว่างเนื้องอกรังไข่แบบเยื่อเมือกที่เป็นชนิดไม่ร้ายแรง ชนิดก้ำกึ่ง และชนิดร้ายแรงของสารบ่งชี้ค่ามะเร็งในเลือด ได้แก่ carcinoembryonic antigen (CEA) cancer antigen 125 (CA-125) และ cancer antigen 19-9 (CA19-9)

วิธีการศึกษา : การศึกษานี้เป็นการศึกษาแบบย้อนหลัง โดยวิเคราะห์ข้อมูลทางคลินิกและพยาธิวิทยาจากผู้ป่วยจำนวน 294 ราย ที่ได้รับการวินิจฉัยว่าเป็นเนื้องอกรังไข่แบบเยื่อเมือก และเข้ารับการผ่าตัดที่โรงพยาบาลมหาราชนครราชสีมา ระหว่างเดือนมกราคม พ.ศ. 2558 ถึง ธันวาคม พ.ศ. 2564 โดยมีการตรวจสารบ่งชี้ค่ามะเร็งในเลือดก่อนการผ่าตัด ได้แก่ CA 19-9, CA-125 และ CEA จากนั้นได้วิเคราะห์ประสิทธิภาพในการวินิจฉัยประเมินโดยใช้ค่า sensitivity specificity positive predictive value (PPV), negative predictive value (NPV) และ receiver operating characteristic (ROC) curve analysis.

ผลการศึกษา : ในกลุ่มผู้ป่วยทั้งหมด พบว่า 164 ราย (ร้อยละ 55.8) มีเนื้องอกชนิดไม่ร้ายแรง 74 ราย (ร้อยละ 25.1) มีเนื้องอกชนิดก้ำกึ่งและชนิดร้ายแรง 56 ราย (ร้อยละ 19.1) ค่า CEA มีความสัมพันธ์กับพยาธิสภาพชนิดก้ำกึ่งหรือร้ายแรงมากที่สุด (risk ratio = 2.3, 95% CI: 1.8-3.0) และมีความแม่นยำในการวินิจฉัยสูงที่สุด (AUC = 0.738) ในขณะที่ CA19-9 และ CA-125 มีค่า AUC ต่ำกว่า (0.679 และ 0.682 ตามลำดับ) เมื่อพิจารณาแต่ละตัวแยกกัน พบว่าสารบ่งชี้ทั้งสามตัวมีค่า sensitivity และ specificity ไม่มาก อย่างไรก็ตาม การใช้ CEA ร่วมกับ CA19-9 ทำให้ค่า specificity สูงถึงร้อยละ 97.2 และค่า PPV ร้อยละ 94.3 ในการวินิจฉัยเนื้องอกชนิดก้ำกึ่งหรือร้ายแรง นอกจากนี้เมื่อสารบ่งชี้ทั้งสามตัวอยู่ในระดับปกติ sensitivity ในการตัดความเป็นไปได้ของมะเร็งอยู่ที่ร้อยละ 81.9 และ NPV อยู่ที่ร้อยละ 70

สรุป : CEA CA19-9 และ CA-125 เป็นสารบ่งชี้ค่ามะเร็งในเลือดที่มีประโยชน์ในการแยกประเภทของเนื้องอกรังไข่แบบเยื่อเมือก แม้ว่าการใช้แต่ละตัวแยกกันจะมีข้อจำกัดในด้านความแม่นยำ แต่การใช้ร่วมกันแบบพหุปัจจัยสามารถเพิ่มความถูกต้องในการวินิจฉัยอย่างมีนัยสำคัญ และช่วยในการตัดสินใจก่อนผ่าตัดได้อย่างมีประสิทธิภาพมากขึ้น

คำสำคัญ : เนื้องอกรังไข่แบบเยื่อเมือก carcinoembryonic antigen (CEA) cancer antigen 125 (CA-125) cancer antigen 19-9 (CA19-9) สารบ่งชี้ค่ามะเร็ง มะเร็งรังไข่ การวินิจฉัย

ABSTRACT

Background : Mucinous ovarian tumors are classified into benign, borderline, and malignant types, each with distinct histologic and surgical implications. Ultrasound can detect these tumors but has limited accuracy in differentiating subtypes. The role of tumor markers carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), and cancer antigen 19-9 (CA19-9) is still under investigation, and more research is needed to determine their diagnostic accuracy and clinical usefulness in the management of ovarian cancer.

Objective : To evaluate the diagnostic performance of serum tumor markers CEA, CA-125, and CA19-9 in distinguishing between benign, borderline, and malignant subtypes of mucinous ovarian tumors.

Methods : This retrospective study analyzed clinical and pathological data from 294 patients diagnosed with mucinous ovarian tumors who underwent surgery at Maharat Nakhon Ratchasima Hospital between January 2015 and December 2021. Preoperative serum levels of CA19-9, CA-125, and CEA were recorded and analyzed. Diagnostic performance was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curve analysis.

Results : Among the patients, 164 (55.8%) had benign tumors, 74 (25.1%) had borderline tumors, and 56 (19.1%) had malignant tumors. Serum CEA showed the strongest association with borderline or malignant pathology (risk ratio = 2.3, 95% CI: 1.8–3.0) and had the highest diagnostic accuracy (AUC = 0.738). CA19-9 and CA-125 had lower AUC values (0.679 and 0.682, respectively). When used individually, all markers had limited sensitivity and specificity. However, the combination of CEA and CA19-9 yielded a specificity of 97.2% and a PPV of 94.3% for diagnosing borderline or malignant tumors. When all three markers were within normal ranges, the sensitivity and NPV for excluding malignancy were 81.9% and 70.0%, respectively.

Conclusions : CEA, CA19-9, and CA-125 are useful serum tumor markers in differentiating subtypes of mucinous ovarian tumors. While individual markers show limited diagnostic performance, a multi-marker approach significantly enhances diagnostic accuracy and supports more informed preoperative decision-making.

Keywords : Mucinous ovarian tumor, CEA, CA-125, CA19-9, tumor markers, ovarian cancer, diagnosis, ROC curve, borderline ovarian tumor, mucinous carcinoma

Background

Mucinous ovarian tumor is a subtype of ovarian tumor characterized by its production of mucin, a glycoprotein that is typically found in mucus-secreting cells[1]. These tumors can range from benign to malignant and are classified based on their biological behavior and histological features.

Mucinous ovarian tumors are histologically classified into three main subtypes based on their biological behavior: mucinous cystadenomas, mucinous borderline ovarian tumors, and mucinous ovarian carcinomas. Mucinous cystadenomas are benign neoplasms that typically present as large, multilocular cystic masses. Mucinous borderline ovarian tumors are considered to have low malignant potential and represent an intermediate form, which may or may not progress to invasive carcinoma. In contrast, mucinous ovarian carcinomas are malignant neoplasms characterized by a higher propensity for recurrence and metastatic spread. Mucinous ovarian tumor usually presents with a huge pelvic mass, with or without symptoms at the diagnostic time.

The ultrasonographic appearance of these tumor subtypes can be similar, making it difficult to differentiate between these conditions based on ultrasound alone. However, there are some characteristic features that can help in the diagnosis[1]. Mucinous cystadenomas typically present as large, well-circumscribed cystic masses with thin, smooth walls and homogeneous mucinous fluid content. Mucinous borderline ovarian tumors may exhibit similar features; however, they often demonstrate thicker cyst walls and the presence of internal septations. In contrast, mucinous ovarian carcinomas are usually identified as complex cystic masses with thick, irregular walls, heterogeneous internal contents, and, in some cases, signs of local tissue invasion or malignant cells within the cystic fluid.

In general, the sensitivity of ultrasonography in detecting ovarian tumors is estimated to be around 70-90%. The specificity of ultrasonography in differentiating between Mucinous cystadenomas, Mucinous borderline ovarian tumors, and Mucinous ovarian carcinomas can vary, with some studies reporting values as low as 60-70% for differentiation between cystadenomas and carcinomas[1].

The surgical approach for Mucinous cystadenomas is typically minimally invasive, such as a laparoscopic or robotic-assisted procedure. The goal of the surgery is to remove the entire tumor and preserve as much normal tissue as possible. In most cases, only the affected ovary and fallopian tube need to be removed, allowing for preservation of the other ovary and uterus.

For Mucinous borderline ovarian tumor, the surgical approach may be more extensive, the excision of suspected peritoneal lesions, omentectomy or appendectomy if the appendix appears abnormal should also be performed.

The surgical approach for mucinous ovarian carcinoma is much more extensive, with the goal of removing as much of the cancer as possible. The procedure may involve a total hysterectomy (removal of uterus and cervix), bilateral salpingo-oophorectomy (removal of both ovaries and fallopian tubes), and lymph node dissection. The extent of the surgery will

depend on the stage of the cancer, the size and location of the tumor, and the patient's overall health

Preoperative counseling for ovarian tumors with signs of malignancy is crucial. The use of tumor markers for the differentiation of mucinous tumors, despite similar clinical presentations and ultrasound findings, is still under question and remains a controversial issue.

CEA, CA12-5, and CA19-9 are tumor markers commonly used in medical research and clinical practice. Elevated levels of CEA, CA12-5, and CA19-9 can be an indicator of various types of malignancy, including colon, pancreas, lung, breast, and gastric cancer.

The sensitivity and specificity of CA19-9 as a screening tool for ovarian carcinoma have been reported to be 50% and 98%, respectively[2].

The sensitivity and specificity of each tumor marker (CA19-9, CA-125 and CEA) for differentiate borderline or malignant mucinous ovarian tumor from mucinous cystadenoma, for CA19-9 were 52.7% and 83.8%, CA-125 were 68.2% and 83.9%, CEA were 31.9% and 90.8%, respectively[3]. Other studies have reported controversial results, and only a few have researched at the relationship between mucinous ovarian tumor subtypes and serum tumor markers[4-11].

The role of these markers in differentiating between different types of ovarian tumors is still under investigation, and more research is needed to determine their diagnostic accuracy and clinical usefulness in the management of ovarian cancer.

Objective:

To evaluate the diagnostic performance of serum tumor markers-carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), and cancer antigen 19-9 (CA19-9) in distinguishing between benign, borderline, and malignant subtypes of mucinous ovarian tumors.

Methods

Retrospective study collected the data from patients who presented with cystic ovarian mass. They were admitted for surgery under the Obstetrics and Gynecology Department, Maharat Nakhon Ratchasima Hospital between January 2015 until December 2021. The study was approved by the Maharat Nakhon Ratchasima Hospital Institutional Review Board (MNRH IRB) on April 20th, 2023, with the certificate number 037/2023.

Patients who had a pathological confirmation of a mucinous ovarian tumor and had preoperative serum levels of CA19-9, CA-125, or CEA recorded were included in the analysis. Patients who did not have complete medical records or who had been diagnosed with a different type of malignancy were excluded.

All the pathological slides were reviewed by a pathologist to confirm the final diagnosis.

The demographic data included age, intraoperative tumor size, pathological results (i.e., benign, borderline or malignant) and serum tumor marker before the surgery (CA19-9, CA-125 and CEA with cut off values at 35 U/mL, 35 U/mL and 4 ng/mL, respectively).

In this study, the data was analyzed using descriptive statistics. The frequency and percentage, mean and standard deviation (SD), or median and interquartile range were calculated, depending on the distribution of the data. The univariate analysis was conducted using either Pearson's chi-squared test or Fisher's exact test for categorical data, and either Student's t-test or the Wilcoxon ranksum (Mann–Whitney U) test for continuous data, as appropriate based on the data's distribution. The diagnostic accuracy of the tumor markers, cut off value, sensitivity and specificity were analyzed using receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was used as a metric to compare the performance of each marker in distinguishing between benign, borderline, and malignant mucinous ovarian tumors. The statistical analysis was conducted using SPSS version 26 software.

Results

The data of mucinous ovarian tumor patients who underwent surgery and preoperative examination for serum CA-19-9, CA-125, or CEA at Maharat Nakhon Ratchasima Hospital during January 2015 until December 2021 revealed 294 records.

This study involved a total of 294 patients, with 164 diagnosed with benign mucinous ovarian tumors (55.8%), 74 with borderline tumors (25.1%), and 56 with mucinous ovarian carcinomas (19.1%). The average age of the patients was 47.9 years. 61.6% of patients had serum CA19-9 levels below 35 U/mL, 49% had CA-125 levels below 35 U/mL, and 64% had CEA levels below 4 U/mL.

The median of tumor size was 13 cm (range 3-40 cm). Twenty patients presented with bilateral tumor (6.8%).

The patients' and tumors' characteristics by pathological classification are demonstrated in Table 1.

Table 1 Baseline characteristics

	Mucinous cystadenoma (n = 164)	Borderline or malignant mucinous ovarian tumor (n = 130)	p-value
Age (years, mean ± SD)	47 ± 15.6	49 ± 15.2	0.27
Size (cm, median ± SD)	12.4 ± 6.3	17.6 ± 8.4	< 0.01
CEA < 4 U/mL	72	42	< 0.01
CEA ≥ 4 U/mL	9	55	
CA125 < 35 U/mL	55	39	< 0.01
CA125 ≥ 35 U/mL	32	66	
CA19-9 < 35 U/mL	63	43	< 0.01
CA19-9 ≥ 35 U/mL	16	50	
Bilateral involvement (n, %)	5 (3%)	15 (11.5%)	0.019

The risk ratio associated with borderline pathology or malignancy in mucinous ovarian tumor are presented in Table 2.

Table 2. Factors associated with borderline pathology or malignancy in mucinous ovarian tumor.

Tumor markers	Risk ratio	95% Confidence interval	p-value
CA19-9	1.9	1.4 - 2.4	<0.0001
CA125	1.6	1.2 - 2.1	0.0006
CEA	2.3	1.8 - 3.0	<0.0001

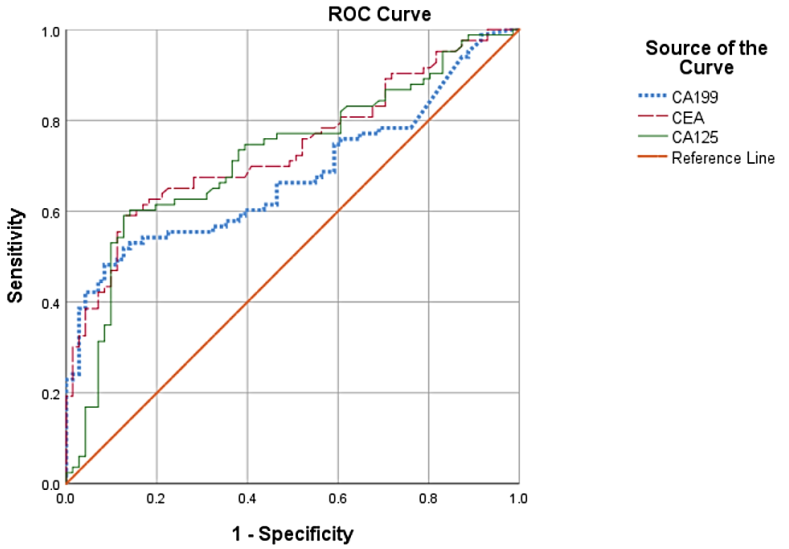
The sensitivity and specificity of each tumor marker (CA19-9, CA-125 and CEA) in borderline or malignant mucinous ovarian tumor for CA19-9 were 53.8% and 79.8%, CA-125 were 62.9% and 63.2%, CEA were 56.7% and 88.9%, respectively.

The diagnostic accuracy of each tumor marker in differentiating between benign and borderline or malignant mucinous ovarian tumors is presented in Table 3. Of the markers compared, CEA showed the best performance with an area under the ROC curve of 0.738, as depicted in Figure 1.

Table 3. Diagnostic performance of each tumor markers for discrimination of borderline or malignant and benign mucinous ovarian tumor

Tumor markers	Sensitivity	Specificity	PPV	NPV	Area under ROC curve
CA19-9	53.8	79.8	75.8	59.4	0.679
CA125	62.9	63.2	67.4	58.5	0.682
CEA	56.7	88.9	85.9	63.2	0.738

Figure 1.



The diagnostic accuracy of tumor marker combination in differentiating between benign and borderline or malignant mucinous ovarian tumors is presented in Table 4.

Table 4. Diagnostic performance of tumor markers combination for discrimination of borderline or malignant and benign mucinous ovarian tumor

Tumor markers (Positive test condition)	Sensitivity	Specificity	PPV	NPV
Either CEA or CA125 was elevated	76.9	57.7	68	68
Either CEA or CA19-9 was elevated	72.9	67.6	72.9	67.6
Either CA125 or CA19-9 was elevated	75.6	55.7	66	66.7
At least one of CEA or CA125 or CA19-9 was elevated	81.9	49.3	65.4	70
Both CEA and CA19-9 were elevated	38.8	97.2	94.3	57
Both CA19-9 and CA125 were elevated	44.4	88.6	81.6	58.3
Both CEA and CA125 were elevated	45	94.9	91.1	59.7

Discussion

Tumor markers play a crucial role in the differential diagnosis and management of ovarian neoplasms. CA125 is the most widely used biomarker for epithelial ovarian cancer, especially serous subtypes, with elevated levels observed in approximately 80% of advanced-stage cases[12].

Mucinous ovarian tumors, comprising benign, borderline, and malignant subtypes, often present with elevated levels of CA19-9 and CEA[2]. These markers are particularly useful in distinguishing primary mucinous ovarian carcinoma from gastrointestinal metastases. For instance, a study from Thailand involving 314 patients found that elevated serum CA19-9, CA125, and CEA levels were significantly associated with malignant or borderline mucinous tumors, with CA125 demonstrating the strongest association[3].

In this study, we found that all of the three serum tumor markers (CA19-9, CA-125, and CEA) had strong association with the tumor pathology. The elevation of the serum CA19-9 (>35 U/mL), CA-125 (>35 U/mL) and CEA (>4 U/mL) was significantly associated with the borderline or malignant mucinous tumor with the risk ratio of 1.9 (95% CI = 1.4–2.4), 1.6 (95% CI = 1.2-2.1) and 2.3 (95% CI = 1.8–3.0), respectively. Furthermore, the serum CEA demonstrated the strongest risk association with borderline or malignancy among those mucinous ovarian tumors, followed by CA19-9 and CA-125. These serum tumor markers also demonstrated good diagnostic performance. The area under ROC curve of CA19-9, CA-125 and CEA was 0.679, 0.682 and 0.738 respectively. Among these markers, the serum CEA had shown the best diagnostic performance, followed by CA19-9 and 12.5. Although the results differed from those of previous studies[3, 5, 10], all tumor markers were still found to be useful in the diagnosis of the borderline or malignant mucinous tumor.

When using a single tumor marker in the diagnosis of borderline or malignant mucinous tumors, we found that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were suboptimal and did not provide sufficient accuracy for reliable clinical decision-making.

However, when we used a combination of tumor markers as showed in Table 4, the diagnostic values improved. In the combination

of CEA and CA19-9, if both tumor markers were positive, the specificity and PPV were 97.2% and 94.3%, respectively.

Furthermore, when all tumor markers tested CEA, CA19-9, and CA-125 were within normal ranges, the likelihood of malignancy was considerably reduced. In such cases, the sensitivity and NPV for excluding a diagnosis of borderline or malignant mucinous tumor were 81.9% and 70.0%, respectively.

Limitations

Several limitations should be acknowledged. First, this was a retrospective study, which may be subject to selection bias and incomplete clinical data. Second, the sample size, although comparable to prior studies, may still limit the generalizability of the findings. Third, tumor marker levels can be influenced by other benign or malignant conditions, potentially confounding the interpretation.

Conclusions

This study highlights the diagnostic value of serum tumor markers CA19-9, CA-125, and CEA in distinguishing borderline or malignant mucinous ovarian tumors from benign tumors. Serum CEA showed the strongest association with tumor pathology and demonstrated the highest diagnostic accuracy, followed by CA19-9 and CA-125. While the performance of individual markers was limited in terms of sensitivity and specificity, their combined use significantly improved diagnostic precision. Notably, positive both of CEA and CA19-9 yielded high specificity and PPV, while the absence of elevation in all three markers offered a reasonable sensitivity and NPV for ruling out malignancy. These findings support the use of a multi-marker approach to improve preoperative risk stratification in patients with suspected mucinous ovarian tumors.

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