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The diagnostic value of determination of serum GOLPH3 associated with CA125, CA19.9 in patients with ovarian cancer

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Abstract. – OBJECTIVE: To evaluate the value of three tumor markers serum Golgi phosphoprotein-3 (GOLPH3), cancer antigen 125 (CA125) and cancer antigen 19-9 (CA19.9) in the diagnosis and postoperative evaluation of ovarian cancer by detecting these three markers.

PATIENTS AND METHODS: A total of 187 patients were studied and included in the ovarian cancer group, benign pelvic mass group, and the normal control group. The levels of serum Golgi phosphoprotein-3 (GOLPH3), cancer antigen 125 (CA125) and cancer antigen 199 (CA19.9) were detected, respectively, and their effects on the diagnosis, evaluation, pathology typing and staging of ovarian cancer were measured.

RESULTS: The sensitivity of the detection of ovarian cancer by GOLPH3 combined with CA125 and CA19.9 was higher than that by a single marker ($p<0.05$). The level of serum GOLPH3 in patients with serous and endometrioid carcinoma was significantly higher than that in patients with mucinous carcinoma, clear-cell carcinoma and germ cell tumor ($p<0.05$). There was no significant statistical difference in serum GOLPH3 level between patients with ovarian malignancies at stage III-IV and those at stage I-II ($p>0.05$). The levels of serum GOLPH3, CA125 and CA19.9 in patients with ovarian malignancies after surgery were significantly lower than those before surgery ($p<0.05$).

CONCLUSIONS: The combined detection by GOLPH3, CA125, and CA19.9 may improve the diagnosis rate of ovarian epithelial cancer. GOLPH3, as a new ovarian cancer tumor marker used in clinical diagnosis, is expected to become an important indicator for the early diagnosis of ovarian cancer and the determination of clinical surgery efficacy.

Key Words
GOLPH3, CA125, CA19.9, Ovarian cancer, Diagnostic value.

Introduction

Ovarian cancer is one of the three major malignant tumors of female genital organs[1]. The histological type of ovarian cancer is complicated. Among them, serous cystadenocarcinoma is the most common type, whose mortality rate ranks first in gynecological malignancies and incidence rate is increasing year by year[2-4].

At present, serum cancer antigen 125 (CA125) is the most widely used epithelial ovarian cancer tumor marker, but the early diagnosis rate of CA125 is low, and it will be increased in some non-malignant diseases to varying degrees, so its specificity to ovarian cancer is not high[5-9]. Therefore, there is a need to find one or more tumor markers in the detection combined with CA125 to improve the early diagnosis rate of ovarian cancer, sensitivity and specificity, which has become the focus of the current study. Golgi phosphoprotein-3 (GOLPH3) is a new ovarian cancer tumor marker, whose level is very low in benign and normal tissues but very high in ovarian cancer, suggesting that it has a certain value in the diagnosis of ovarian cancer[10-12]. The current research on GOLPH3 is relatively less, and the specific clinical significance of it also needs to be further verified.

This study aimed to conduct a combined detection by three-tumor markers GOLPH3, CA125 and cancer antigen 199 (CA19.9), to explore its value in the diagnosis and postoperative evaluation of ovarian cancer.

Patients and Methods

Patients

We selected patients with the average age of 52.94±14.06 years old who were admitted to Shanxian Central Hospital for surgery from January 2015 to January 2017 due to pelvic masses. According to the confirmation of postoperative pathology, the patients were divided into the ovarian cancer group (n=46) and the benign pelvic mass group (n=91). 50 healthy females who received the physical examination in physical ex-

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amination center of our hospital in the same period were selected as the control group. All patients with ovarian malignancies were the initial cases. They received no radiotherapy, chemotherapy or other treatments during 3 months before surgery, and patients with the history of other systematic cancers history or endocrine diseases were excluded. This study was approved by the Ethics Committee of Shanxian Central Hospital. Signed written informed consents were obtained from all participants before the study.

Methods

Samples detection: enzyme-linked immunosorbnent assay (ELISA) was used to detect the serum GOLPH3 levels in all groups (Thermo Fisher Scientific, Waltham, MA, USA). All serum samples were taken from 3 mL fasting elbow vein blood at the preoperative 2-3 d and 1 month after surgery, and the collection method of samples in the control group was the same as that of patients. The levels of CA125 and CA19.9 in serum were measured by enhancedchemiluminescence immunoassay (ECI).

Determination of results: the reference value of serum GOLPH3 was 0-150 pg/mL, and GOLPH3>150 pg/mL represented that the result was positive; the reference value of CA125 was 0-35 U/mL, and CA125>35 U/mL represented that the result was positive; the reference value of CA19.9 was 0-37 U/mL, and CA19.9>37 U/mL represented that the result was positive. The determination method of the positive rate of the combined detection by serum GOLPH3, CAl25 and CAl99: the positive result of any one marker represented the result of a combined detection by any two markers was positive, and the negative results of both markers represented the result of the combined detection was negative; the positive result of any one marker represented the result of a combined detection by three markers was positive, and the negative results of all three markers represented the result of the combined detection was negative.

Statistical Analysis

All statistics were performed using Statistical Product and Service Solutions (SPSS Version X; IBM, Armonk, NY, USA) 19.0 software. *t*-test was performed for the comparison of mean value, and x^2-test for the significant difference between count data. Comparisons between groups were conducted using least significant difference (LSD) method. $p<0.05$ suggested the difference was statistically significant.

Results

Comparisons of the Levels of Serum GOLPH3, CA125 and CA19.9 as Well as Positive Rate Among the Groups

The overall difference in the levels of serum GOLPH3, CA125 and CA19.9 in the ovarian cancer group, the benign pelvic mass group (benign group) and the control group (healthy female group) were significant ($p<0.05$). Results of pairwise comparisons showed that the differences in the levels of serum GOLPH3, CA125 and CA19.9 in the ovarian cancer group were statistically significant compared with those in the benign group and the control group ($p<0.05$). The differences in serum GOLPH3 and CA19.9 between the benign group and the control group were not significant ($p<0.05$), but there was statistically significant difference in the level of serum CA125 between the benign group and the control group ($p<0.05$) (Table I).

The positive rates of serum GOLPH3 and CA125 in the ovarian cancer group were 71.74% and 76.09%, respectively, and there was no significant difference between the two markers ($\chi^2=2.016$, $p=0.454$), but there were statistically differences in the positive rate of CA19.9 (36.96%) compared with that of the other two markers in the same group ($\chi^2=9.273$, $p=0.001$; $\chi^2=10.712$, $p=0.003$). The positive rates of serum CA125 and CA19.9 in the benign group were 30.77% and 10.99%, respectively. There were statistically significant differences in the positive rate of GOLPH3 compared with that of

Table I. Comparisons of the levels of serum GOLPH3, CA125 and CA19.9 as well as positive rate among groups.

	No.	GOLPH3 (pg/ml)		CA125 (U/ml)		CA19.9 (U/ml)	
		$\bar{x}\pm s$	N (%)	$\bar{x}\pm s$	N (%)	$\bar{x}\pm s$	N (%)
Ovarian cancer group	46	420.52±281.36	33 (71.74)	396.48±231.29	35 (76.09)	96.13±59.98	17 (36.96)
Benign group	91	69.46±27.52	0 (0)	28.56±17.34	28 (30.77)	20.13±10.79	10 (10.99)
Control group	50	65.65±22.84	0 (0)	12.48±8.47	0 (0)	10.85±6.32	0 (0)

CA125 and CA19.9 (χ^2=24.874, p<0.001, χ^2=16.095, p<0.001). In other words, the false positive rates of CA125 and CA19.9 were significantly higher than that of GOLPH3 in the benign group (Table I).

Comparisons of the Sensitivity and Specificity of the Combined Detection of Ovarian Cancer by Serum GOLPH3, CA125 and CA19.9

The sensitivity of the combined detection of ovarian cancer by GOLPH3 and CA125 and that by GOLPH3, CA125 and CA19.9 was 90.8% and 94.6%, respectively, and the specificity was 81.6% and 80.1%, respectively. Statistical analysis was conducted for the comparison between the two combined detections, and the results showed that the differences were not statistically significant (χ^2=20.649, p=0.128). Compared with the single marker detection, the detection combined with GOLPH3 could improve the sensitivity of detection, and the difference was statistically significant (p<0.05); the detection specificity was not reduced (Table II).

Comparisons of the Levels of Serum GOLPH3, CA125 and CA19.9 in Patients with Different Histological Types of Ovarian Malignancies

The levels of serum GOLPH3 in patients with serous carcinoma and endometrioid carcinoma were 440.23±229.52 pg/mL and 450.49±264.19 pg/mL, respectively, which were significantly higher than those in patients with mucinous carcinoma, clear cell carcinoma or germ cell tumor (80.05±49.81 pg/mL, 140.72±90.08 pg/mL and 50.86±34.50 pg/mL, respectively); the level of serum CA125 in patients with serous carcinoma was 408.34±210.14 U/mL, which was significantly higher than that in patients with mucinous carcinoma, endometrioid carcinoma, clear cell carcinoma or germ cell tumor (87.79±79.27 U/mL, 136.24±80.35 U/mL, 59.05±39.13 U/mL and 42.14±31.97 U/mL, respectively); the level of serum CA19.9 in patients with mucinous carcinoma was 122.24±30.16 U/mL, which was significantly higher than that in patients with serous carcinoma, endometrioid carcinoma, clear cell carcinoma or germ cell tumors (42.26±14.38 U/mL, 37.82±14.06 U/mL, 22.46±16.98 U/mL and 14.99±8.57 U/mL) (Table III).

Table II. Comparisons of the sensitivity and specificity of the combined detection of ovarian cancer by serum GOLPH3, CA125 and CA19.9 (%).

Tumor marker	Sensitivity (%)	Specificity (%)
GOLPH3	72.5	100
CA125	79.2	81.4
CA19.9	40.1	88.7
GOLPH3+CA125	90.8	81.6
GOLPH3+CA19.9	83.3	89.0
GOLPH3+CA125+CA19.9	94.6	80.1

Comparisons of the Levels of Serum GOLPH3, CA125 and CA19.9 as Well as Positive Rates in Patients with Ovarian Malignancies at Different Clinical Stages

The serum GOLPH3 level in patients with ovarian malignancies at stage III-IV was 430.17±200.46 pg/mL, and compared with that at stage I-II, the difference was not statistically significant (T=0.534, p=0.722). The levels of serum CA125 and CA19.9 in patients with ovarian malignancies at stage III-IV were 403.42±187.54 U/mL and 106.48±10.62 U/mL, respectively, and compared with those at stage I-II (82.41±61.16 U/mL and 19.89±12.05 U/mL), respectively, the differences were statistically different (T=9.387, p<0.001; T=15.281, p<0.001). The positive rates of GOLPH3 and CA125 in patients with ovarian malignancies at stage I-II were 45.45% and 36.36%, respectively, and the difference between the two markers was not statistically significant (p=0.45). The positive rates of GOLPH3 and CA125 in patients with ovarian malignancies at stage III-IV were 77.14% and 88.57%, respectively, and the difference between the two markers was not statistically significant (p=0.326) (Table IV).

Table III. Comparisons of the levels of serum GOLPH3, CA125 and CA19.9 in patients with different histological types of ovarian malignancies ($\bar{x}$±s).

Histological Type	No.	GOLPH3 (pg/ml)	CA125 (U/ml)	CA19.9 (U/ml)
Serous carcinoma	20	440.23±229.52	408.34±210.14	42.26±14.38
Mucinous carcinoma	6	80.05±49.81	87.79±79.27	122.24±30.16
Endometrioid carcinoma	14	450.49±264.19	136.24±80.35	37.82±14.06
Clear Cell carcinoma	3	140.72±90.08	59.05±39.13	22.46±16.98
Germ cell tumor	3	50.86±34.50	42.14±31.97	14.99±8.57

Table IV. Comparisons of the levels of serum GOLPH3, CA125 and CA19.9 as well as positive rates in patients with ovarian malignancies at different clinical stages.

Clinical Stage	No.	GOLPH3 (pg/ml)		CA125 (U/ml)		CA19.9 (U/ml)	
		$\bar{x}$±s	N (%)	$\bar{x}$±s	N (%)	$\bar{x}$±s	N (%)
I-II	11	389.04±168.29	5 (45.45)	82.41±61.16	4 (36.36)	19.89±12.05	0 (0)
III-IV	35	430.17±200.46	27 (77.14)	403.42±187.54	31 (88.57)	106.48±10.62	17 (48.57)

Comparisons of the Levels of Serum GOLPH3, CA125 and CA19.9 in Patients with Ovarian Malignancies Before and After Surgery

The levels of serum GOLPH3, CA125 and CA19.9 in patients with ovarian cancer after surgery were 185.74±99.18 pg/mL, 200.46±101.53 U/mL and 43.18±22.15 U/mL, respectively, and compared with that in patients with ovarian cancer before surgery, the differences were statistically significant (T=5.153, p=0.003; T=4.874, p=0.001; T=8.096, p=0.001) (Table V).

Discussion

Ovarian cancer is one of the common malignant tumors of gynecology, and the incidence rate in recent years has shown a clear upward trend. Early detection of ovarian cancer is the most promising way to extend patient survival and improve patient quality of life. Unfortunately, there is no good tumor marker that has a high sensitivity and specificity to early ovarian cancer[1-4]. This study aimed to investigate the clinical value of the detection by a single marker GOLPH3, CA125 or CA19.9 and the combined detection by all of them in the diagnosis of ovarian cancer as well as before and after surgery by detecting the changes in serum levels of GOLPH3, CA125 and CA19.9 in normal women, benign pelvic masses and before and after ovarian cancer surgery.

Previous studies have shown that CA125 is a relatively better marker of epithelial ovarian cancer with the highest sensitivity to serous carcinoma[5-9]. This study showed that the level of serum C125 in the ovarian cancer group was significantly higher than that in the benign pelvic mass group and the control group, suggesting that CA125 is a relatively better tumor marker of ovarian cancer with the highest sensitivity to serous cystadenocarcinoma. However, the study also suggested that serum CA125 determination was used for the diagnosis of ovarian cancer, whose sensitivity and specificity was poor, and false positive rate as well as early diagnosis rate, was low.

Studies have shown that CA19.9 is highly expressed in epithelial ovarian cancer, which can be used for the diagnosis and prognosis of ovarian borderline and malignant tumors and so on[13,14]. In this study, the level of serum CA19.9 in the review 1 month after surgery was significantly lower than that before surgery. Therefore, it was considered that CA19.9 might be an important index for postoperative monitoring of ovarian cancer and the presence or absence of recurrence. In addition, this study showed that the level of CA19.9 in patients with ovarian cancer at stage III-IV was significantly higher than that at stage I-II, indicating that preoperative determination of serum CA19.9 levels might contribute to clinical staging, but the diagnosis sensitivity of CA19.9 to early ovarian cancer at stage I-II.

Studies have suggested that, as a new tumor marker, GOLPH3 is a good marker of ovarian cancer, especially a relatively more stable tissue marker of ovarian serous cystadenocarcinoma and endometrioid carcinoma[10-12]. The detection of GOLPH3 in this work showed that the level of serum GOLPH3 was significantly higher than that in the benign disease group and the control group, and the sensitivity of it was 72.5%, which

Table V. Variation of the levels of serum GOLPH3, CA125 and CA19.9 in patients with ovarian malignancies before and after surgery ($\bar{x}$±s).

Group	GOLPH3 (pg/ml)	CA125 (U/ml)	CA19.9 (U/ml)
Before surgery	420.52±281.36	396.48±231.29	96.13±59.98
After surgery	185.74±99.18	200.46±101.53	43.18±22.15

was equivalent to that of CA125 (79.2%). The ROC^{AUC} of GOLPH3 was 0.935, which further showed that GOLPH3 has a higher ability to diagnose ovarian cancer. In the study, there was no positive GOLPH3 in patients with benign pelvic masses and healthy women, which overcame the limitation of the false positive rate of CA125, indicating that the ability of GOLPH3 was stronger than that of CA125 in diagnosing ovarian benign and malignant diseases. This was of significance in the differential diagnosis of ovarian tumors. This study showed that the level and the positive rate of GOLPH3 in patients with serous cystadenocarcinoma and endometrioid carcinoma were significantly higher than those in patients with other types of cancer in the same group, further indicating that GOLPH3 was relatively more sensitive to serous cystadenocarcinoma and endometrial carcinoma. At the same time, the detection in this study showed that the level of serum GOLPH3 1 month after tumor resection was significantly lower than that before surgery, suggesting that GOLPH3 might be used as an important index for the treatment and recurrence of postoperative monitoring of ovarian cancer. This paper also showed that the difference in the level of serum GOLPH3 between the patients with ovarian cancer at stage III-IV and at stage I-II was not statistically significant, suggesting that the expression level of GOLPH3 might be not related to clinical staging. In addition, the positive rate of GOLPH3 in patients with ovarian cancer at stage I-II was significantly higher than that of CA125 and CA19.9, suggesting that GOLPH3 might be one of the early screening indexes of ovarian cancer.

The detection by a single tumor marker in the early diagnosis of ovarian cancer is lack of sensitivity and specificity, so the combined detection by multi-tumor markers is often applied clinically. The results of this study showed that the sensitivity of the combined detection of GOLPH3, CAl25 and CA19.9 detection was significantly better than that of the combined detection by GOLPH3 and CAl25 as well as that by GOLPH3 and CA19.9. The results of the present study have shown that GOLPH3 has a high specificity in the identification of ovarian tumors, which may be an important index whose value for the early diagnosis of ovarian cancer is better than that of CA125, so it has been considered that the combined detection by these two markers may improve the diagnosis rate of early ovarian cancer, but the final conclusion still needs to be further confirmed by expanding the sample size.

Conclusions

GOLPH3 is one of the most promising indexes for ovarian cancer diagnosis, surgical outcome judgment and postoperative monitoring, and the detection combined GOLPH3 with CA125 and CA19.9, and can improve the diagnosis rate of early ovarian cancer. The relative research is still relatively less, and the sample size needs to be further expanded. Besides, the in-depth research combined with multi-center needs to be conducted to assess its potential application in the clinical diagnosis and treatment of ovarian cancer.

Conflict of Interest

The authors declared no conflict of interest.

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