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Original Article

Effect of different metastasis patterns on the prognosis of patients with stage III high-grade serous ovarian cancer

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Abstract: To investigate the effect of different metastatic patterns of stage III high-grade serous ovarian cancer on the patient prognosis. The clinical data of 134 patients with Stage III, high-grade serous ovarian cancer diagnosed in The Affiliated Hospital of Qingdao University from January 2018 to April 2020 were retrospectively collected, and the patients were grouped according to metastasis mode. Patients with simple lymph node metastasis (SLNM) were included in the SLNM group, and patients with simple abdominal implantation alone and patients with abdominal metastasis combined with lymph node metastasis were all in the abdominal metastasis (AM) group. The prognosis of the two groups was analyzed. Of the 134 enrolled patients, complete datasets from 128 were successfully collected. There were 20 cases of SLNM (15.63%) and 108 cases of AM (84.37%). Initial CA125, initial HE4, and whether neoadjuvant chemotherapy was used were compared between the two groups ($P < 0.05$). According to the chemotherapy results, patients was divided into two groups: chemotherapy remission and uncontrolled, including 111 patients with chemotherapy remission and 17 patients with uncontrolled chemotherapy. According to the criteria of relapse after complete completion of chemotherapy and clinical remission, 91 cases relapsed, 20 cases did not relapse, of which 78 cases were platinum-sensitive, and 13 were platinum-resistant relapses. There were 4 recurrence cases in SLNM group (4.40%) and 87 recurrence cases (95.60%) in AM group ($P < 0.05$). The recurrence sites of 91 patients were analyzed, including 52 cases (57.14%) in the peritoneum, 11 cases (12.09%) in distant regions, 9 cases (9.89%) in lymph nodes, 19 cases (20.88%) in the peritoneum and lymph nodes. Significant differences were noted in the two groups' peritoneum, lymph node, and distance ($P < 0.05$). The two groups had significant differences in progression-free survival, overall survival, and 3-year survival (all $P < 0.05$). Initial HE4 levels, chemotherapy sensitivity, and SLNM are independent prognostic factors for Stage III high-grade serous ovarian cancer patients. Initial HE4 level < 233.7 pmol/l and chemotherapy sensitivity were protective factors, indicating a good prognosis. Patients in the SLNM group had lower initial CA125 and HE4 levels and higher survival rates. Initial HE4 levels and chemotherapy sensitivity are independent factors affecting prognosis in Stage III high-grade serous ovarian cancer patients.

Keywords: Serous ovarian cancer, lymphatic metastasis, abdominal metastasis, simple lymph node metastasis, prognosis

Introduction

Ovarian cancer is the third most common gynecological reproductive system malignant tumor after cervical and endometrial cancer. Furthermore, the ovarian cancer incidence ranks third among female reproductive system tumors, while the mortality rate ranks first [1]. The most frequently occurring type of ovarian cancer is epithelial ovarian cancer, which constitutes approximately 85-90% of cases; of these, serous cancer is the most prevalent [2]. Due to advancements in medical technology, the cure rate for ovarian cancer has significantly improved. However, many patients, particularly those with advanced-stage ovarian cancer, still face poor prognoses. In such cases, the 5-year survival rate is only 47% [3]. Sinukumar et al. [4] reported the prognosis of patients with superficial lymph node metastasis that patients with positive lymph node metastasis were found to have lower invasiveness. Addi-

tionally, their data showed that those patients' progression-free survival and overall survival were longer than Stage IIIc patients with intraperitoneal implantation metastasis. Furthermore, the prognosis is similar to that of Stage IIIA patients, indicating that these patients may represent a unique subgroup of Stage IIIc patients. Liu et al. and Hai et al. [5, 6] compared the clinical results of ovarian cancer patients with lymph node metastasis and those with intraperitoneal implantation metastasis. Their data showed that compared with ovarian cancer patients with intraperitoneal implantation metastasis, ovarian cancer patients with only lymph node metastasis have a better prognosis and higher survival rate. Moreover, it was found that compared with Stage IIIC and IIIB patients, Stage IIIA patients with positive lymph node metastasis alone had a better prognosis recovery. Rosendahl et al. [7] confirmed that the revised FIGO staging has a higher guiding significance for patients with only lymph node metastasis than patients with intraperitoneal implantation metastasis. Generally, ovarian cancer patients with simple lymph node metastasis have a better prognosis; however, some researchers have also proposed different theories [8]. Additionally, their data showed that the 5-year survival rate between ovarian cancer patients with intraperitoneal implantation metastasis and those with simple lymph node metastasis was similar.

The prognosis and survival of ovarian cancer with different modes of metastasis remain controversial. People in different regions may have different demographic characteristics, genetic backgrounds, and environmental factors, the inclusion of Chinese samples can provide region-specific data and increase the representativeness and extrapolation of the study. Therefore, in this study, we compared the clinical and pathological differences of patients with Stage III serous ovarian cancer and different metastatic modes and further analyzed the prognostic factors of Chinese patients. These data will be helpful in better predicting the prognosis of patients with ovarian cancer.

Materials and methods

Materials

Clinical data of patients with Stage III high-grade serous ovarian cancer diagnosed in The Affiliated Hospital of Qingdao University from January 2018 to April 2020 were retrospectively collected. The patients were grouped according to metastasis mode. Patients with simple lymph node metastasis were included in the simple lymph node metastasis (SLNM) group, and patients with simple abdominal implantation alone and patients with abdominal metastasis combined with lymph node metastasis were all in the abdominal metastasis (AM) group.

Inclusion and exclusion criteria

Inclusion criteria: Patients aged ≥ 18; Patients without history of other malignant tumors before surgery; Patientswho met the Stage III criteria for clinical staging of ovarian cancer established by FIGO; Patientswho had undergone a whole-body imaging evaluation, including CT scan, MRI, or PET-CT to determine the pattern of metastasis; Patients who had a postoperative pathological diagnosis of high-grade serous ovarian cancer; Patients with a complete standard medical history, including previous medical history, preoperative laboratory and imaging findings, and intraoperative data; Patients with ordinary consciousness and normal communication ability.

Exclusion criteria: Patients with stage FIGOI-II and IV epithelial ovarian cancer; Patients with other epithelial types of ovarian cancer, such as mucinous, endometrioid, or clear cell carcinoma; Patients with other malignant tumors; Patients with incomplete clinical data; Or patients who lost to follow-up.

Outcome measurements

Patients' clinicopathological data, such as age, initial CA125 and HE4 level, whether received neoadjuvant chemotherapy, number of chemotherapy, satisfaction with surgery, and the recurrence and chemosensitivity of patients, were extracted from the electronic medical system of Affiliated Hospital of Qingdao University. The criteria utilized to assess chemosensitivity and resistance involved the timeframe of relapse following the completion of chemotherapy and the achievement of clinical remission. Patients who experienced relapse more than six months after the completion of chemotherapy and achieved clinical remission were considered clinically platinum-sensitive.

Table 1. Comparison of clinical case characteristics between the two groups

Clinicopathological characteristics	SLNM (n=20)	AM group (n=108)	t/χ^2	P
Age (years)	58.74±8.85	58.51±9.26	0.103	0.918
Initial CA125 (u/ml)	211.36±23.36	269.69±22.37	10.639	< 0.001
Initial HE4 (pmol/l)	185.32±20.08	287.31±21.13	19.975	< 0.001
Neoadjuvant chemotherapy or not				
Yes	6	63	5.452	0.020
No	14	45		
Chemotherapy Frequency (times)	7.24±2.98	7.81±2.75	0.840	0.402
Surgical satisfaction				
Satisfied	16	76	0.774	0.379
Dissatisfied	4	32		

SLNM, simple lymph node metastasis; AM, abdominal metastasis.

In contrast, patients who failed to meet the above criteria or relapsed within six months were classified as resistant to platinum-based chemotherapy [9]. Recurrence was defined as the presence of two or more of the following conditions: serum CA125 level was abnormally increased, imaging examination revealed recurrent lesions, peritoneal fluid and/or pleural effusion was observed, gynecological examination found a mass, or the occurrence of unexplained intestinal obstruction [10]. Biochemical recurrence was determined by the level of tumor markers, such as increased CA125, without imaging or clinical evidence of tumor recurrence [11]. The primary outcomes assessed in this study wereprogression-free survival (PFS), overall survival (OS), and 3-year overall survival. These outcomes served as key measures to evaluate the efficacy of the treatment or intervention being investigated. Additionally, secondary outcomes such as the recurrence rate, factors that influence prognosis, and the overall survival of patients were assessed.

Statistics

SPSS 26.0 was used to analyze the data. Measurement data were expressed by (Mean ± Standard Deviation) ($\bar{x} \pm s$), and the inter-group comparisons were performed by independent sample t-test. Count data are expressed as percentages [n (%)] and were compared using the χ^2 test. A ROC curve was used to calculate the cut-off value of measurement data. Numerical variables were converted into categorical variables and were assessed using the Cox proportional regression risk model for multivariate survival analysis. *P*-values less than 0.05 indicated statistical significance.

Results

Comparison of clinical case characteristics between the two groups

Of 134 patients enrolled, 128 data sets were successfully collected, with 6 patients withdrawn from the study due to medical issues. Of the finally included patients, 20 cases (15.63%) had simple lymph node metastasis, and 108 were AM cases (84.37%). Clinical characteristics such as age, number of chemotherapies, and satisfaction with surgery were similar between the two groups (all $P > 0.05$). However, significant differences were observed in initial CA125 and HE4 levels and whether being administered with neoadjuvant chemotherapy between the two groups (all $P < 0.05$) (**Table 1**).

Comparison of chemotherapy sensitivity and recurrence rates between two groups

According to patient-specific chemotherapy data, the patients were divided into chemotherapy remission and uncontrolled chemotherapy groups, with 111 cases in the chemotherapy remission group and 17 cases in the uncontrolled chemotherapy group. Among the 111 cases with clinical remission, there were 91 cases of recurrence, including 78 cases of platinum-sensitive relapse and 13 cases of platinum-resistant relapse, and 20 cases without. There were 4 cases of recurrence (4.40%) in SLNM group and 87 cases (95.60%) in AM group. The recurrence rate between the two groups was statistically significant ($P < 0.05$) (**Table 2**).

Table 2. Comparison of chemotherapy sensitivity and recurrence rates between two groups

Chemotherapy outcome	n	SLNM (n=20)	AM (n=108)	χ^2	*P*
Uncontrolled chemotherapy	17	2	15	0.222	0.638
Chemotherapy remission	111	18	93		
No recurrence	20	14	6		
Recurrence	91	4	87	30.111	< 0.001
platinum-sensitive	78	4	74	0.697	0.404
platinum-resistant	13	0	13		

SLNM, simple lymph node metastasis; AM, abdominal metastasis.

Table 3. Comparison of recurrence sites between two groups

Recurrent site	Number of cases	SLNM (n=4)	AM group (n=87)	χ^2	*P*
Peritoneum	52	0	52	5.579	0.018
Lymph node	9	1	8	1.072	0.301
Peritoneum + lymph nodes	19	1	18	0.043	0.836
Distance	11	2	9	5.659	0.017

SLNM, simple lymph node metastasis; AM, abdominal metastasis.

Table 4. Comparison of survival rates between two groups [n (%)]

Index	SLNM (n=18)	AM group (n=93)	χ^2	*P*
Progression-free survival rate	14 (77.78)	6 (6.45)	51.940	< 0.001
Overall survival rate	15 (83.33)	20 (21.51)	26.703	< 0.001
3-year overall survival rate	17 (94.44)	29 (31.18)	24.871	< 0.001

SLNM, simple lymph node metastasis; AM, abdominal metastasis.

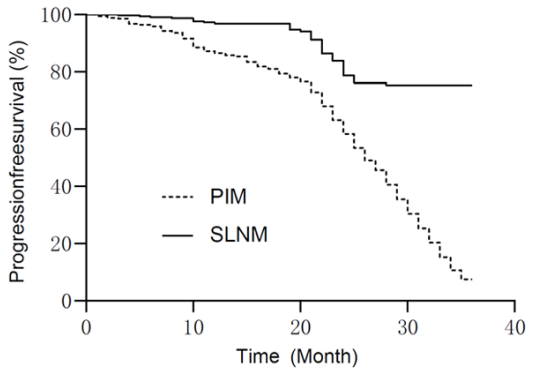

Figure 1. Progression free survival curve. SLNM, simple lymph node metastasis; AM, abdominal metastasis.

Comparison of recurrence sites between two groups

Next, the recurrence sites of the 91 patients were analyzed. Of them, 52 cases (57.14%) were in the peritoneal area, 11 cases (12.09%) had a distant recurrence, 9 cases were in lymph node (9.89%), and 19 cases (20.88%) had recurrence at the peritoneal and lymph node sites. The recurrence sites of the two groups of patients were compared, and the differences were statistically significant ($P < 0.05$). The recurrence site of SLNM were mostly in lymph nodes and distant areas, while that in the AM group were peritoneum and peritoneum + lymph nodes (**Table 3**).

Comparison of survival rates between two groups

Using the Kaplan-Meier survival analysis curve, the 3-year survival status of two groups of patients was analyzed. The difference in PFS, OS, and 3-year overall survival between the two groups of patients was statistically significant (all $P < 0.05$), with SLNM having higher survival rates (**Table 4** and **Figures 1**-**3**).

COX proportional risk regression analysis

According to the cut-off values of CA125 (861.5 U/ml) and HE4 (233.7 pmol/L) obtained from ROC curve, the patients with initial CA125 ≥ 861.5 U/mL was divided into a ≥ 861.5 U/mL group and the others were assigned into a < 861.5 U/mL group; So as for the initial level of HE 4 (**Table 5** and **Figure 4**).

According to the 2021 Diagnosis and Treatment Recommendations for Ovarian Malignant Tumors, ovarian cancer patients who have undergone satisfactory tumor cell reduction surgery will undergo a total of 6 courses of chemotherapy. Therefore, the chemotherapy frequency was divided into groups with > 6 doses and ≤ 6 doses.

Next, a univariate COX proportional regression analysis was performed on the above clinicalpathological factors. Then, using the significant influencing factors from that analysis, a multivariate COX proportional regression analysis

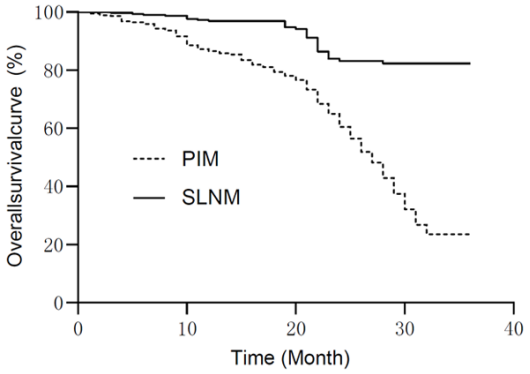

Figure 2. Overall survival curve. SLNM, simple lymph node metastasis; AM, abdominal metastasis.

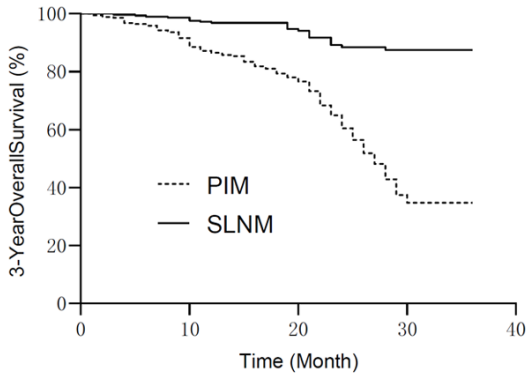

Figure 3. 3-year overall survival curve. SLNM, simple lymph node metastasis; AM, abdominal metastasis.

was performed to identify the most significant independent contributing prognostic factors. The results showed that initial HE4 levels, chemotherapy sensitivity, and SLNM were independent prognostic factors for Stage III advanced serous ovarian cancer patients. Additionally, the analysis indicated that the initial HE4 level < 233.7 pmol/L and chemotherapy sensitivity are protective factors, predicting a better patient prognosis (**Table 6**).

Discussion

Most advanced ovarian cancer patients are accompanied by pelvic organ metastasis or distant metastasis, and the number of patients receiving satisfactory tumor cell reduction surgery or chemotherapy is limited, resulting in a lower survival rate. The stage of malignant tumor disease is related to prognosis, and the increase in clinical stages often reflects the deterioration of the disease prognosis. In 2013, FIGO revised the clinical staging of ovarian cancer and increased the number of subphases to better capture a larger spectrum of disease. However, there is controversy regarding FIGO staging and its indicative role in patient prognosis. This study aimed to explore the difference between ovarian cancer patients with simple lymph node metastasis and those with AM and analyzed the relationship between patient prognosis and clinical-pathological factors. The results showed significant differences between the SLNM and AM groups regarding initial CA125 and HE4 levels and whether neoadjuvant chemotherapy was used. Further analysis was conducted on the recurrence and drug sensitivity of the two groups, which indicated that, compared with AM patients, patients with simple lymph node metastasis had a lower recurrence rate and higher drug sensitivity.

CA125 and HE4 are common tumor markers in clinical practice, and their serum levels are related to disease progression [10]. Furthermore, previous studies have suggested that CA125 is the best tumor marker for diagnosing ovarian cancer [11]. Other study has shown that CA125 can cause damage to tumor immune function, indicating that CA125 plays an important role in the progression of cancer diseases [12]. Previous studies have reported that platinum-resistant and partially platinum-sensitive ovarian cancer patients have higher levels of CA125 than platinum-sensitive patients [13]. In agreement with these data, this study suggests that detecting serum CA125 levels can predict patient chemotherapy drug resistance. Another study found that detecting serum CA125 levels can determine the degree of AM accompanied by malignant ascites [14]. Research has shown that the higher the serum CA125 level in patients with serous ovarian cancer, the lower the survival rate. Additionally, all studies have shown that serum CA125 levels are associated with AM in ovarian cancer, and the higher the CA125 level, the poorer the prognosis of patients [15]. However, CA125 has certain limitations as an early diagnostic marker. A report stated that only half of advanced ovarian cancer patients with obvious symptoms have significantly increase CA125 levels; therefore, the sensitivity and specificity of diagnosis are low if

Table 5. Initial CA125, HE4 horizontal ROC curve

Factor	Sensitivity	Specificity	AUC	Cut-off	95% CI
Initial CA125 (U/ml)	56.0%	55.2%	0.571	861.5	0.522~0.619
Initial HE4 (pmol/L)	54.8%	66.2%	0.592	233.7	0.531~0.658

SLNM, simple lymph node metastasis; AM, abdominal metastasis; ROC, receiver operator characteristic.

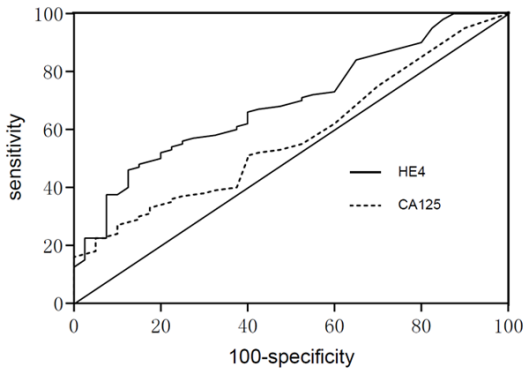

Figure 4. Initial CA125, HE4 horizontal ROC curve. ROC, receiver operator characteristic.

assessed by CA125 in the absence of other clinical markers or evidence [16].

Research reports on HE4 as a clinically relevant tumor marker for ovarian cancer has been increasing in recent years. Data showed that, compared with CA125, HE4 has higher sensitivity and specificity and that HE4 levels are associated with ovarian cancer progression [17]. Multiple studies have shown that the expression of HE4 is closely related to the biological behavior of cancer cells and that HE4 induces tumor cells to develop resistance to anticancer drugs, which can activate AKT and other related signaling pathways, further improving patient survival rate [18, 19]. Another study suggests that the expression of HE4 in ovarian cancer tissue is related to patient prognosis and recurrence [20]. Zheng et al. [21] found that compared with advanced ovarian cancer patients with normal serum HE4 levels, advanced ovarian cancer patients with elevated serum HE4 levels have significantly shorter progression-free survival. Through multiple factor COX proportional risk regression analysis, this study showed that the initial HE4 level is an independent prognostic factor for patients with Stage III advanced serous ovarian cancer. The abnormal increase in HE4 levels is likely to lead to drug resistance and is related to the recurrence of ovarian cancer disease, shortening patient survival time and affecting prognosis. Therefore, detecting serum levels and dynamic changes of CA125 and HE4 in clinical practice can serve as diagnostic markers and predict patients' prognoses.

In this study, the recurrence rate in the AM group was significantly higher than that in the SLNM group, and the lymph node recurrence rate in the SLNM group was higher than that in the AM group, indicating that the AM group was more inclined towards peritoneal recurrence and had a lower recurrence rate in the lymph node area. In clinical practice, simple lymph node metastasis is relatively rare, but the lymph node recurrence rate is more significant than AM. Due to limitation, this study only observed the 3-year survival of patients; however, we found differences in the progression-free survival and overall survival between the two groups of patients. Compared with the AM group, SLNM patients had a more extended survival period. Further analysis of prognostic factors for Stage III advanced serous ovarian cancer patients was conducted, and initial HE4 level and chemotherapy sensitivity were found to be independent prognostic factors for Stage III advanced serous ovarian cancer patients.

However, this study also has limitations. It is a retrospective study that cannot exclude the influence of confounding factors. Therefore, it is necessary for future studies to use multiple-factor analysis methods to correct confounding factors. Additionally, future prospective studies must be designed to obtain more robust evidence and further explore the prognostic factors of advanced stage III serous ovarian cancer patients.

In summary, compared with AM patients with serous ovarian cancer, serous ovarian cancer patients with simple lymph node metastasis have lower initial CA125 and HE4 levels. At the same time, these patients' progression-free and overall survival rates are also higher, and initial HE4 levels and chemotherapy sensitivity are independent prognostic factors.

Table 6. COX proportional risk regression analysis

Clinical pathological factors	Single factor			Multi-factor		
	Risk ratio HR	95% *CI*	*P*	Risk ratio HR	95% *CI*	*P*
Age (years)	1.106	0.856-1.431	0.431			
Initial CA125	1.345	1.042-1.743	0.022	0.903	0.616-1.328	0.605
Initial HE4	2.273	1.571-3.276	0.000	1.695	1.134-2.537	0.010
Chemotherapy sensitivity	0.371	0.283-0.484	0.000	0.317	0.214-0.467	0.000
Received neoadjuvant chemotherapy or not	1.931	1.477-2.525	0.000	1.508	0.914-2.481	0.105
Number of chemotherapies	1.533	1.148-2.041	0.005	1.032	0.624-1.701	0.908
Surgical satisfaction	0.973	0.727-1.295	0.841			
Transfer mode	1.245	1.011~3.325	0.000	1.512	1.185~2.613	0.000

COX, cyclooxygenase.

Disclosure of conflict of interest

None.

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