

Impact of Ovarian Metastatectomy on Survival Outcome of Colorectal Cancer Patients with Ovarian Metastasis: A Retrospective Study

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Background: Ovarian metastasis from colorectal cancer (CRC) is rare and lacks standard treatment. The benefit of metastatectomy remains to be elucidated. This study was conducted to assess the impact of metastatectomy on survival outcome and explore prognostic factors in ovarian metastatic CRC patients.

Methods: Information of ovarian metastatic CRC patients between January 2008 and December 2017 were collected retrospectively from database of West China Hospital, Sichuan University. Kaplan–Meier method was used to estimate disease-specific survival (DSS) after diagnosis of ovarian metastasis, and multivariate Cox regression analysis was applied to identify prognostic factors.

Results: Totally, 68 female patients from a cohort of 2170 cases were eligible. The median age at diagnosis was 46.5 years. The median DSS was 25.0 months (95% confidence interval (CI): 21.0–29.0 months). Kaplan–Meier analysis and Log rank test showed that complete resection of ovarian metastases (median DSS: 33.0 months) could significantly prolong patients' survival time, compared with palliative and no resection (median DSS: 20.0 months and 22.0 months, respectively), regardless of systemic chemotherapy ($P < 0.05$). Multivariate analysis demonstrated regional lymph nodes metastasis of primary tumor (hazard ratio (HR): 3.438, 95% CI: 1.094–10.810, $P = 0.035$), primary tumor resection (HR: 6.436, 95% CI: 1.770–23.399, $P = 0.005$), differentiation grade (HR: 0.272, 95% CI: 0.107–0.693, $P = 0.006$), complete resection of ovarian metastases (vs palliative resection: HR: 17.091, 95% CI: 3.040–96.099, $P = 0.001$; vs no resection: HR: 9.519, 95% CI: 1.581–57.320, $P = 0.014$), and systemic chemotherapy (HR: 3.059, 95% CI: 1.089–8.595, $P = 0.034$) were independent prognostic factors.

Conclusion: Complete resection of ovarian metastases could independently predict favorable survival in ovarian metastatic CRC, while palliative resection could not improve patients' prognosis compared with no resection.

Keywords: ovarian metastasis, colorectal cancer, metastatectomy

Plain Language Summary

There is no standard treatment for ovarian metastatic CRC, which happens rarely and has poor prognosis. To date, the role of surgery for ovarian metastases still remains unclear. We conducted this retrospective study to evaluate the benefit of metastatectomy and explore prognostic factors. In total, 68 patients newly diagnosed with ovarian metastatic CRC were identified from a cohort of 2170 female cases with metastatic CRC. Results showed that the median disease-specific survival was 25.0 months (95% CI: 21.0–29.0 months). Compared with palliative and no resection of ovarian metastases, complete resection could significantly prolong patients' survival time, regardless of systemic chemotherapy ($P < 0.05$). Multivariate

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analysis identified regional lymph nodes metastasis of primary tumor, primary tumor resection, differentiation grade, complete resection of ovarian metastases, and systemic chemotherapy as independent prognostic factors. Our study indicated that limited ovarian metastases could be the candidates for surgery, which could help clinicians in making individualized treatment strategies.

Introduction

Ovarian metastasis is relatively rare in colorectal cancer (CRC) female patients, with an incidence of about 0.8–7.4%.¹ Metastatic ovarian tumors from CRC commonly manifest as cyst-solidary masses on imaging examination, which are indistinguishable from primary ovarian cancer.² It is reported that about 4%–29% CRC patients with ovarian metastases are initially misdiagnosed and receive surgery as primary ovarian malignancies.^{3–5} Pathological diagnosis of CRC ovarian metastasis generally needs assistance of immunohistochemistry, which is characterized as cytokeratin 7 (CK7) -/CK20+/caudal-type homeobox transcription factor-2 (CDX2) +/-carbohydrate antigen 125 (CA125) -/paired box gene 8 (PAX8)-.^{1,6,7}

In recent years, despite rapid progress in treatment strategies of advanced CRC, ovarian metastasis from CRC has poor prognosis. Studies have demonstrated primary resistance of ovarian metastases to systemic chemotherapy, with an objective response rate (ORR) less than 20%, which is much worse than that of metastases in other organs.^{8,9} Although some retrospective studies with small sizes have indicated survival benefit of ovarian metastasectomy, the role of surgery for ovarian metastases still remains unclear.¹⁰ The poor prognosis of ovarian metastasis may contribute to easy misdiagnosis and lack of standard treatment. In this study, we summarized clinicopathological characteristics, survival outcome and prognostic factors of ovarian metastatic CRC patients in a single institution during a 10-year period.

Patients and Methods

Patient Selection

Female patients who were newly diagnosed with ovarian metastatic CRC between January 2008 and December 2017 were identified retrospectively from the database of Cancer Center at West China Hospital, Sichuan University. Patients' information and treatment history were obtained through medical records. All patients were followed-up to July 31, 2018.

Data of the patients were collected including age at the time of diagnosis with ovarian metastasis, menopausal status,

pretreatment serum carcinoembryonic antigen (CEA) level, primary tumor location, initial T and N stage of primary tumor, time interval between diagnosis of primary tumor and that of ovarian metastasis (metachronous vs synchronous), size of ovarian metastases, combined metastases outside ovaries, ascites, surgical methods of ovarian metastases (no resection vs palliative resection vs complete resection), systemic chemotherapy and response evaluation. For patients received surgical resection of ovarian masses, pathological diagnoses were confirmed by immunohistochemistry staining of ovarian specimens (CK7-/CK20+/CDX2+/CA125-/PAX8-). In the current study, the time interval between diagnosis of primary tumor and that of ovarian metastasis exceeding 3 months was defined as metachronous ovarian metastasis, otherwise as synchronous metastasis. Palliative resection of ovarian metastases meant microscopic or macroscopic residual disease in ovaries (R1 or R2 resection), while complete resection referred to no residual disease left in ovaries (R0 resection).

This study was approved by the West China Hospital, Sichuan University Ethic Committee for Clinical Investigation. And all methods were performed in accordance with the relevant guidelines and regulations.

Statistical Analysis

Median disease-specific survival (DSS) was estimated with Kaplan–Meier method, which was calculated from the date of diagnosis with ovarian metastasis to death (caused by cancer) or last follow-up time. Death caused by CRC was considered as endpoint event. Patients who were still alive at last follow-up time or who had died of other causes were censored. Log rank test was used to compare survival time of different groups and a multivariate Cox proportional hazard regression model was established to determine the associations between survival time and other factors such as age, menopausal status, primary tumor location, ascites, surgical methods of metastases and systemic chemotherapy et al. Statistical tests were two sided and $P < 0.05$ was considered statistically significant. SPSS Statistics 22.0 (IBM, Armonk, NY, USA) was applied to perform all the statistical analyses.

Results

Patient Characteristics

Patients' clinical characteristics are summarized in Table 1. In total, 68 patients newly diagnosed with ovarian metastatic CRC were identified from a cohort of 2170 female patients with metastatic CRC, including 54.4% premenopausal patients. Hence, the incidence of ovarian metastases in female

Table I Characteristics and Univariate Disease-Specific Survival Analysis of Patients with Ovarian Metastatic CRC

Variables		Number of Patients (%)	mDSS (95% CI)	P
Age	≤46.5 years	33 (48.5)	27.0 (22.5–31.5)	0.185
	>46.5 years	35 (51.5)	23.0 (19.2–26.8)	
Menopausal status	Premenopausal	37 (54.4)	31.0 (24.4–37.6)	0.039
	Postmenopausal	31 (45.6)	21.0 (13.1–28.9)	
CEA level	≤ULN	19 (27.9)	48.0 (23.7–72.3)	0.003
	>ULN	49 (72.1)	22.0 (19.7–24.3)	
Primary tumor location	Rectum	16 (23.5)	29.0 (17.1–41.0)	0.515
	Colon	52 (76.5)	25.0 (21.0–29.0)	
T stage of primary tumor*	T2+T3	35 (51.5)	26.0 (23.1–28.9)	0.784
	T4	33 (48.5)	23.0 (13.7–32.3)	
N stage of primary tumor*	Negative	14 (20.6)	31.0 (22.2–39.8)	0.350
	Positive	54 (79.4)	25.0 (20.2–29.8)	
Primary tumor resection	Yes	62 (91.2)	27.0 (21.8–32.2)	0.002
	No	6 (8.8)	10.0 (0.0–28.0)	
Histological type of primary tumor	Adenocarcinoma	47 (69.1)	25.0 (19.8–30.2)	0.147
	Mucinous adenocarcinoma+ signet-ring cell carcinoma	21 (30.9)	29.0 (16.8–41.2)	
Differentiation grade of primary tumor	Well differentiated	38 (55.9)	25.0 (18.0–32.0)	0.894
	Poorly differentiated	30 (44.1)	26.0 (20.4–31.6)	
Synchronous metastasis	Yes	32 (47.1)	22.0 (18.4–25.6)	0.193
	No	36 (52.9)	29.0 (18.4–39.6)	
Bilateral or unilateral metastasis	Bilateral	27 (39.7)	21.0 (18.9–23.1)	0.114
	Unilateral	41 (60.3)	26.0 (20.8–31.2)	
Combined with metastases outside ovaries	Yes	56 (82.4)	23.0 (17.8–28.2)	0.022
	No	12 (17.6)	40.0 (35.8-NA)	
Ascites	Yes	36 (52.9)	25.0 (19.2–30.8)	0.755
	No	32 (47.1)	25.0 (16.5–33.5)	
Peritoneal metastasis	Yes	28 (41.2)	20.0 (9.4–30.6)	0.032
	No	40 (58.8)	31.0 (23.8–38.2)	

(Continued)

Table 1 (Continued).

Variables		Number of Patients (%)	mDSS (95% CI)	P
Liver metastasis	Yes	19 (27.9)	21.0 (12.1–29.9)	0.007
	No	49 (72.1)	29.0 (21.6–36.4)	
Lung metastasis	Yes	12 (82.4)	23.0 (20.0–26.0)	0.158
	No	56 (17.6)	27.0 (18.2–35.8)	
The largest diameter of ovarian metastasis	≤8.0cm	36 (52.9)	29.0 (17.7–40.3)	0.645
	>8.0cm	32 (47.1)	25.0 (22.3–27.7)	
Surgery of ovarian metastasis	Complete resection	29 (42.6)	33.0 (21.4–44.6)	0.002
	Palliative resection	28 (41.2)	20.0 (13.1–26.9)	
	No resection (chemotherapy only)	11 (16.2)	22.0 (19.5–24.5)	
Systemic chemotherapy	Yes	48 (70.6)	27.0 (20.8–33.2)	0.204
	No	20 (29.4)	23.0 (9.1–36.9)	
Total		68 (100)	25.0 (21.0–29.0)	-

Notes: *In patients without primary tumor resection, the reported T and N stage were clinically evaluated based on imaging techniques; Bold text, significant P values (<0.05).

Abbreviations: CRC, colorectal cancer; mDSS, median disease-specific survival; CEA, carcinoembryonic antigen; ULN, upper limit of normal.

metastatic CRC was 3.1%. The median age at diagnosis of ovarian metastasis was 46.5 years. The median time from primary cancer diagnosis to ovarian metastasis detection was 4.5 months. And the median largest diameter of ovarian lesions was 8.0 cm. There were 32 (47.1%) cases presented with synchronous ovarian metastasis, while 36 (52.9%) with metachronous metastasis. Twelve (17.6%) patients had metastases confined in the ovaries, whereas the left 56 (82.4%) patients presented with extraovarian metastases in liver, lung, peritoneum, bone, etc. when diagnosed with ovarian metastatic CRC. More than half of the patients (52.9%) had ascites and 41.2% had peritoneal metastasis. As to treatment approach, 42.6% of all cases underwent complete resection of ovarian metastases, 41.2% of cases received palliative resection, and the left 16.2% patients did not undergo ovarian metastatectomy. Most patients (70.6%) received systemic chemotherapy after diagnosis of ovarian metastasis. In the group of no resection, all the patients received systemic chemotherapy, while in the groups of complete and palliative resection, 55.2 and 75% patients received chemotherapy, respectively. Patients refused chemotherapy for a variety of reasons, such as unsatisfactory postoperative recovery, concerning about adverse reactions and cost. All the patients had good performance status when

diagnosed with ovarian metastasis, with Eastern Cooperative Oncology Group (ECOG) scores of 0–1.

Survival Analyses for Different Groups

In total, the median DSS after diagnosed with ovarian metastasis was 25.0 months (95% confidence interval (CI) =21.0–29.0 months). Univariate survival analysis results are listed in [Table 1](#). In this study, we classified surgical methods of ovarian metastases into three groups, ie, no resection (chemotherapy only), palliative resection (R1 and R2 resection) and complete resection (R0 resection). Applying Kaplan–Meier method, we found that “complete resection group” showed significantly longer DSS than that of the other two groups (“complete resection group” vs “palliative resection group”: 33.0 vs 20.0 months, $P=0.000$; “complete resection group” vs “no resection group”: 33.0 vs 22.0 months, $P=0.026$, [Figure 1](#)), while median DSS of “palliative resection group” was similar to that of “no resection group” (20.0 vs 22.0 months, $P=0.630$, [Figure 1](#)). These results suggested that complete resection of metastatic ovaries predict better survival in CRC patients.

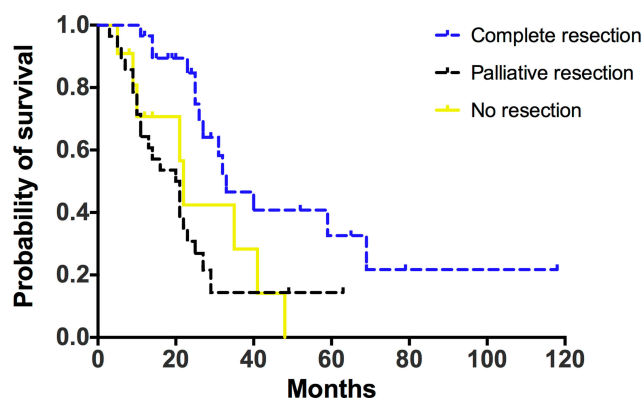


Figure 1 Disease-specific survival of patients with different surgical methods of ovarian metastases.

Stratified analysis revealed that in patients without systemic chemotherapy, the median DSS of complete resection group was significantly longer than that of palliative resection group (26.0 vs 11.0 months, $P=0.001$, Table 2, Figure 2A). In patients receiving systemic chemotherapy, complete resection also prolonged patients' survival time (vs palliative resection: 69.0 vs 21.0 months, $P=0.002$; vs no resection: 69.0 vs 22.0 months, $P=0.007$), while palliative resection could not improve survival outcome compared with no resection (21.0 vs 22.0 months, $P=0.993$, Table 2, Figure 2B).

Prognostic Factors Associated with Survival

Using multivariate Cox proportional hazard regression analysis, we determined the associations between survival and multiple variables such as age, menopausal status, the levels of CEA, primary tumor location, T and N stage of primary tumor, histological type, differentiation grade, primary tumor resection, ascites, synchronous metastasis, bilateral metastasis, size of ovarian metastases, peritoneal metastasis, liver metastasis, lung metastasis, surgical methods of ovarian

metastases and systemic chemotherapy. The results demonstrated that regional lymph nodes metastasis of primary tumor (hazard ratio (HR): 3.438, 95% CI: 1.094–10.810, $P=0.035$), primary tumor resection (HR: 6.436, 95% CI: 1.770–23.399, $P=0.005$), differentiation grade (HR: 0.272, 95% CI: 0.107–0.693, $P=0.006$), complete resection of ovarian metastases (vs palliative resection: HR: 17.091, 95% CI: 3.040–96.099, $P=0.001$; vs no resection: HR: 9.519, 95% CI: 1.581–57.320, $P=0.014$), and systemic chemotherapy (HR: 3.059, 95% CI: 1.089–8.595, $P=0.034$) were independent factors for predicting survival outcome (Table 3).

Discussion

In the current study, we found that in ovarian metastatic CRC, complete resection of ovarian metastases was an independent prognostic factor for favorable survival. Although palliative resection of ovaries could relieve symptoms such as abdominal distension and pain, it failed to improve DSS compared with no resection.

Previous studies have demonstrated ovarian metastases from CRC are resistant to systemic chemotherapy,^{6,9} which is possibly associated with specific gene mutations.^{11,12} Goéré et al⁸ analyzed chemotherapy response in 23 patients with metastatic (ovarian and extra-ovarian) CRC, and found that ovarian metastases were less responsive to chemotherapy compared to other sites. The objective response rate (ORR) of ovarian metastases was 0% and disease control rate (DCR) was 13%, in contrast, ORR and DCR of measurable extraovarian metastases were, respectively, 35% and 65%. Another study of 33 patients conducted by Lee et al⁹ also indicated lower ORR of ovarian metastases compared with extraovarian metastases (18.2% vs 33.3%, $P < 0.001$).

Considering resistance to chemotherapy of ovarian metastases, researchers tried to investigate the benefit of

Table 2 Survival Comparison for Patients Receiving Different Methods of Ovarian Metastatectomy Stratified by Chemotherapy

Chemotherapy	Surgery of Ovarian Metastasis	Number of Patients	mDSS (95% CI)	Complete Resection	Palliative Resection	No Resection
				P	P	P
No	Complete resection	13	26.0 (16.9–35.1)	–	0.001	–
	Palliative resection	7	11.0 (5.9–16.1)	0.001	–	–
Yes	Complete resection	16	69.0 (0.0–140.3)	–	0.002	0.007
	Palliative resection	21	21.0 (18.0–24.0)	0.002	–	0.993
	No resection	11	22.0 (19.5–24.5)	0.007	0.993	–

Note: Bold text, significant P values (<0.05).

Abbreviations: mDSS, median disease-specific survival; CI, confidence interval.

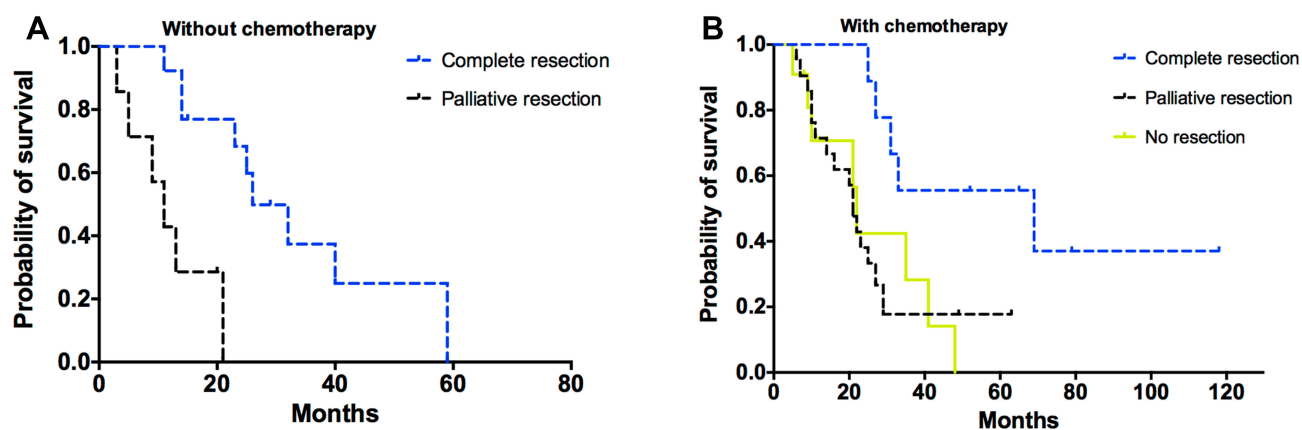


Figure 2 Disease-specific survival of patients receiving different surgical methods of ovarian metastases stratified by systemic chemotherapy. (A) Without chemotherapy, (B) receiving chemotherapy.

metastasectomy for survival. The retrospective study performed by Lee et al⁹ demonstrated that CRC patients with ovarian metastases received an oophorectomy before

chemotherapy survived significantly longer than those without an oophorectomy (28.1 vs 21.2 months, $P=0.015$). Additionally, multivariate analysis indicated that no

Table 3 Multivariate Cox Regression Analysis of Ovarian Metastatic CRC Patients

Variables		HR (95% CI)	P
Age	>46.5 years	I (Reference)	0.398
	≤46.5 years	0.490 (0.094–2.560)	
Menopausal status	Postmenopausal	I (Reference)	0.825
	Premenopausal	0.817 (0.137–4.891)	
CEA level	>ULN	I (Reference)	0.251
	≤ULN	0.523 (0.173–1.582)	
Primary tumor location	Rectum	I (Reference)	0.881
	Colon	0.960 (0.567–1.628)	
T stage of primary tumor*	T2+T3	I (Reference)	0.050
	T4	2.374 (1.000–5.634)	
N stage of primary tumor*	Negative	I (Reference)	0.035
	Positive	3.438 (1.094–10.810)	
Primary tumor resection	Yes	I (Reference)	0.005
	No	6.436 (1.770–23.399)	
Histological type of primary tumor	Adenocarcinoma	I (Reference)	0.363
	Mucinous adenocarcinoma+ signet-ring cell carcinoma	1.522 (0.616–3.765)	

(Continued)

Table 3 (Continued).

Variables		HR (95% CI)	P
Differentiation grade of primary tumor	Poorly differentiated Well differentiated	I (Reference) 0.272 (0.107–0.693)	0.006
Synchronous metastasis	No Yes	I (Reference) 2.478 (0.836–7.343)	0.102
Bilateral or unilateral metastasis	Bilateral Unilateral	I (Reference) 0.999 (0.408–2.445)	0.998
Combined with metastases outside ovaries	Yes No	I (Reference) 0.890 (0.190–4.157)	0.882
Ascites	No Yes	I (Reference) 1.859 (0.803–4.303)	0.147
Peritoneal metastasis	No Yes	I (Reference) 1.121 (0.435–2.889)	0.813
Liver metastasis	Yes No	I (Reference) 0.560 (0.214–1.463)	0.237
Lung metastasis	Yes No	I (Reference) 0.677 (0.222–2.063)	0.493
The largest diameter of ovarian metastasis	>8.0cm ≤8.0cm	I (Reference) 0.697 (0.315–1.546)	0.375
Surgery of ovarian metastasis	Complete resection Palliative resection No resection (chemotherapy only)	I (Reference) 17.091 (3.040–96.099) 9.519 (1.581–57.320)	0.001 0.014
Systemic chemotherapy	Yes No	I (Reference) 3.059 (1.089–8.595)	0.034

Notes: *In patients without primary tumor resection, the reported T and N stage were clinically evaluated based on imaging techniques; Bold text, significant *P* values (<0.05).

Abbreviations: CRC, colorectal cancer; mDSS, median disease-specific survival; CEA, carcinoembryonic antigen; ULN, upper limit of normal; CI, confidence interval; HR, hazard ratio.

oophorectomy was an independent prognostic factor associated with poorer survival (RR=1.954, 95% CI=1.220–3.130, *P*=0.005). This survival benefit of metastasectomy in ovarian metastatic CRC was confirmed by other retrospective studies too.^{13–18} However, a study published in

2017¹⁹ suggested that patients treated with surgery of ovarian metastases and chemotherapy did not have better survival compared with those treated with chemotherapy alone (23 vs 28 months, *P*=0.376). Furthermore, Jiang et al²⁰ analyzed the impact of residual disease on survival in metastatic ovarian

cancer patients (mainly originated from gastric cancer and CRC) who underwent metastasectomy. They found that visible residual disease after metastasectomy independently predicted poorer survival ($P<0.01$). Since the above studies were of small sizes and based on retrospective data, the role of metastasectomy in ovarian metastatic CRC still remains controversial. In our study, we found that complete resection of ovarian metastases could predict better survival (DSS=33.0 months), while palliative and no resection of ovaries were factors of poorer prognosis ($P<0.05$).

There were some limitations in this study, such as retrospective data, small sample size and single-center cohort. And due to small sample size, the differences of baseline situation (such as immunity, performance status) among the three groups may be overlooked. However, the large cohort and complete clinical information of our study confirmed the rarity of ovarian metastasis with an incidence of 3.1%, indicated the survival benefit of complete resection of ovarian metastases and concluded several prognostic factors such as regional lymph nodes metastasis of primary tumor, primary tumor resection, differentiation grade, surgical methods of ovarian metastases and systemic chemotherapy. Our study suggested that limited ovarian metastases could be the candidates for surgery, which could help clinicians in making individualized treatment strategies. Well-designed prospective trial is warranted to verify this viewpoint.

Abbreviations

CRC, colorectal cancer; DSS, disease-specific survival; OS, overall survival; CK7, cytokeratin 7; CDX2, caudal-type homeobox transcription factor-2; CA125, carbohydrate antigen 125; PAX8, paired box gene 8; CEA, carcinoembryonic antigen; CT, computed tomography; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; DCR, disease control rate; RR, rate ratio; ULN, upper limit of normal; ECOG, Eastern Cooperative Oncology Group.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval and Informed Consent

Written informed consent for the use of patient information in our study was obtained from all patients at the time

of admission as a routine practice at West China Hospital, Sichuan University. And this study was approved by the West China Hospital, Sichuan University Ethic Committee for Clinical Investigation.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential competing interests.

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