Clinics in Surgery

Research Article
Published: 17 Jun, 2019

Optimal Surgical Procedure for Ovarian Metastases from Colorectal Cancer based on a Retrospective Analysis

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Abstract

Background and Objectives: The incidence of ovarian metastases from colorectal cancer (CROM) is 2.1% to 14.2%, and the prognosis is poor. This study aimed to identify optimal surgical procedure for CROM through analysis of the clinicopathological characteristics of such patients and the efficacy of resection for ovarian metastases.

Methods: We retrospectively analyzed the records of 222 patients who were diagnosed with CROM and underwent surgery between June 2006 and December 2015 at the Fudan University Cancer Center, Shanghai, China.

Results: The median Overall Survival (OS) time after ovarian metastasectomy was 30.4 months, and the 5-year OS rate was 29.4%. The 5-year OS rate was significantly higher in patients who underwent R0 resection (41%) vs. R1/2 resection (17%, p=0.001). In patients who had unilateral ovarian metastases and underwent R0 resection, bilateral oophorectomy provided no significantly different OS time in comparison to unilateral oophorectomy (p=0.967). In patients without uterine metastases who underwent R0 resection, there was no significant difference between those who underwent hysterectomy and those who did not (p=0.340).

Conclusion: R0 resection of CROM has better OS rates and times than does R1/2 resection. Young women with unilateral ovarian metastases who want to preserve their ovarian function could undergo unilateral oophorectomy. For R0 resection, hysterectomy is unnecessary when the uterus is not involved.

Keywords: Colorectal cancer; Ovarian metastases; Metastasectomy

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Received Date: *29 Apr 2019*
Accepted Date: *13 Jun 2019*
Published Date: *17 Jun 2019*

Citation:
Song W, Huang D, Guo T, Sheng W, Cai S,Wu Y, et al. Optimal Surgical Procedure for Ovarian Metastases from Colorectal Cancer based on a Retrospective Analysis. Clin Surg. 2019; 4: 2475.

Introduction

Colorectal Cancer (CRC), as one of the most common malignancies, is also the most frequently seen cancer among non-gynecologic malignancies that result in ovary metastasis. CRC Ovarian Metastasis (CROM) has an incidence ranging from 2.1% up to as high as 14.2%, and the patients typically present combined extra-ovarian metastases, i.e., both of ovarian and extra-ovarian metastases, rather than isolated ovarian metastases [1-5].

As compared to the CRC patients with extra-ovarian metastases, those with ovarian metastases usually have a lower survival rate, and are less responsive to chemotherapy [6]. Surgical oophorectomy performed as a therapeutic strategy, showing a higher survival rate than chemotherapy according to previous studies [4,7]. Aggressive surgical treatment may benefit patients with CROM, as demonstrated by studies respectively reporting a median Overall Survival (OS) time of 23, 31, 34.9, and 36 months for CROM patients having received ovarian metastasectomy [1,8-11]. However, these studies were retrospective nature with small sample sizes and short-term follow-ups, and therefore are less convincible for evaluating the exact benefits of the surgeries. Although a prospective study would be the best option for assessing the surgical management for ovarian metastasis, collecting samples enough for statistical analysis is a big challenge due to the relatively low incidence and the inoperable condition for most patients with CROM. Aiming to analyze the oncologic outcomes of the surgical procedures, identify the factors associated with the prognosis, and reveal the best options for CROM patients, we carried out a comprehensive retrospective study with the largest sample size

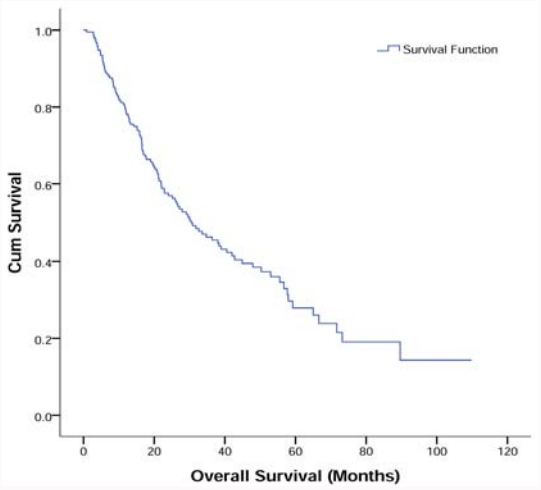

Figure 1: Kaplan-Meier survival curves for overall survival (OS) after oophorectomy in all 222 patients. The median OS was 30.4 months.

so far in this field, in which data of 222 patients having undergone surgery for CROM were collected from a single institution.

Methods

Clinical data collection: Based on the postoperative histopathology, we retrospectively analyzed 222 patients who had undergone resection for ovarian metastases from primary CRCs between June 2006 and December 2015 at the Fudan University Cancer Center, Shanghai, China. Patients without a histopathological diagnosis of CROM, or with other noncolorectal adenocarcinoma were excluded.

Clinical and pathological information was collected from electronic medical records, including age, location of the primary tumor, and presence of combined metastases, pathological pattern, tumor size, and nodal status of the primary tumor, T category and classification for the residual tumor. Postoperative survival of the patients was tracked by telephone follow-ups. This study complied with Ethical Standards and was approved by the Ethics Review Committee of Fudan University Shanghai Cancer Center.

Statistical analysis: Kaplan-Meier method was used to calculate survival. Log-rank test was employed in univariate analysis to explore the association between clinically relevant variables and the OS, and the variables with statistical significance (≤ 0.05) were then introduced into a multivariate analysis using the Cox proportional hazards regression model, with the estimates presented as Hazard Ratio (HR) at 95% Confidence Interval (CI). The significance level was set at 5% for each analysis, and all calculations were performed using SPSS 22 software (IBM SPSS statistics 22).

Results

Clinicopathological features: As shown in Table 1, the clinicopathological analysis revealed a mean age of 49.2 years old (range, 21 to 80 years old) at diagnosis, with 124 (55.8%) women aged <50 years old. Notably, the primary tumors in all the patients were categorized into T3 or T4, predominantly T4 (133 patients, 88.67%). Peritoneal dissemination was detected in 97 patients (43.7%), and lymph node involvement in 108 (76.1%) patients. The number of cases with unilateral or bilateral ovarian metastases was approximately equal to each other. About 57 (34.1%) women had isolated ovarian metastases, in contrast to 165 (65.9%) who had developed combined extra-ovarian metastases. Analyses of the two groups (ovarian *vs.* extra-ovarian metastases) using Chi-square test showed no significant difference (p>0.05) in any of the factors as listed in Table 1. Grossly complete resection (R0), as an option for metastasis confined to the pelvis, was performed in 95 (42.8%) patients.

Univariate and multivariate analysis: Univariate analysis was conducted to identify clinical and pathological characteristics associated with OS (Table 2), with a result indicating three factors to be correlated with significantly increased OS--R0 resection, isolated ovarian metastases and hysterectomy. Multivariable analysis by entering these factors into a Cox proportional hazards regression model confirmed the strong association between the three factors and a longer OS (Table 3). However, further exploration in the R0 resection sub-group revealed no factors significantly associated with a longer OS (Table 2).

Treatment outcomes and associated factors: The median survival time of the entire study population after resection of the ovarian metastases was 30.4 months. The OS rate was 45.4% at 3 years and 29.4% at 5 years (Figure 1).

As demonstrated in Figure 2A, comparative analysis showed a significantly shorter median survival time (21.2 months) and lower 5-year OS rate (22.4%) in the sub-group with combined metastases (165 patients) as compared to the one without combined metastases (57 patients; 59.2 months; 48.7%) (HR, 2.027; 95% CI, 1.079-3.810; p=0.028).

Compared with R1/2 resection sub-group (127 patients) in the multivariate analysis, the R0 resection sub-group (95 patients) exhibited a better performance in the median survival time (16.5 months *vs.* 56.7 months) and a significantly higher 5-year OS rate (14.7% *vs.* 41.7%) (Figure 2B), implying a strong association between R0 resection and a higher OS (HR, 0.427; 95% CI, 0.257-0.709; P=0.001).

Among the 95 patients who underwent R0 resection, metastasis was synchronous with the primary tumor in 39 patients and metachronous in 56 patients. The median survival time was 56.7 months and 57.9 months, and the 5-year OS rate 47.1% and 36.9%, respectively, for the synchronous and metachronous sub-groups (Figure 3A). There was no significant difference in the OS rate between the two sub-groups (p=0.415, Table 2).

As is shown in Figure 3B, cross-over analysis of the patients with unilateral metastases (59 cases) and with bilateral metastases (36 cases) among the R0 resection sub-group revealed no significant difference in median survival time (65.0 *vs.* 55.3 months) and 5-year OS rate (35.5% *vs.* 55.1%) (p=0.795, Table 2). Moreover, among the patients with unilateral metastases in R0 resection sub-group, 5-year OS rate for unilateral oophorectomy (22 patients) and bilateral oophorectomy (36 patients) was 41.7% and 27.2%, respectively (Figure 3C), also failed to show a remarkable difference (Log-Rank Mantel-Cox, p=0.967). However, metastasis was found in the other ovary in three patients respectively at 11, 17, and 32 months after receiving unilateral oophorectomy. Following another oophorectomy, one patient died at 41 months after the first unilateral oophorectomy, one was still alive at 19 months, and the other survived for 72 months before loss to follow-up.

Among the patients without uterine metastases in R0 resection

Table 1: Characteristics of 222 patients with ovarian metastases from colorectal cancers.

Characteristic	Patients (%)	Patients (%)		
		Isolated (n=57)	Combined (n=165)	p-Value
Age at resection of ovarian metastases	49.4 (21 to 80) Median age (range)			0.256
≤50 years	124 (55.8)	36 (62.1)	88 (53.3)	
>50 years	98 (44.2)	21 (37.9)	77 (46.7)	
Chrolonogy				0.198
Synchronous	91 (40.0)	27 (46.4)	64 (38.8)	
Metachronous	131 (60.0)	30 (53.6)	101 (61.2)	
Location of the CRC				0.229
Left-side colon	65 (32.0)	19 (35.8)	-30.7	
Right-side colon	85 (41.9)	17 (32.1)	68 (45.3)	
Rectum	53 (26.1)	17 (32.1)	36 (24.0)	
Pathological pattern of the CRC				0.654
Adenocarcinoma	126 (70.4)	35 (72.9)	91 (69.4)	
Mucinous adenocarcinoma	53 (29.6)	13 (27.1)	40 (30.6)	
T stage				0.498
T3	17 (11.3)	4 (8.7)	13 (12.5)	
T4	133 (88.7)	42 (92.3)	91 (87.5)	
Lymph node involvement with the CRC				0.517
-	34 (23.9)	10 (33.3)	24 (23.5)	
+	108 (76.1)	30 (66.7)	78 (76.5)	
Ovarian site of the metastases				0.305
Left ovary	50 (22.5)	15 (26.3)	35 (21.2)	
Right ovary	59 (26.6)	18 (31.6)	41 (24.8)	
Bilateral	113 (50.9)	24 (42.1)	89 (54.0)	
Ovary size	9.91cm (1 cm to 27 cm) median size (range)			0.894
≤ 10 cm	112 (57.4)	28 (60.9)	84 (56.4)	
>10 cm	83 (42.6)	18 (39.1)	65 (43.6)	
Pathological pattern of ovarian metastases				0.318
Adenocarcinoma	160 (75.1)	41 (80.4)	119 (73.5)	
Mucinous adenocarcinoma	53 (24.9)	10 (19.6)	43 (26.5)	
Hysterectomy				0.227
Yes	93 (41.9)	20 (35.1)	73 (44.2)	
No	129 (58.1)	37 (64.9)	92 (55.8)	
Peritoneal dissemination				
+	97 (43.7)			
-	125 (56.3)			
Residual tumor classification				
R0	95 (42.8)			
R1/2	127 (57.2)			

Note: Isolated: Isolated Ovarian Metastases; Combined: Combined Extraovarian Metastases; p-value: Chi-square Test; Synchronous: Defined as Ovarian Metastases Diagnosed at the Same Time

sub-group, unilateral or bilateral oophorectomy was performed for 45 patients and bilateral oophorectomy plus hysterectomy for 36 patients. There was also no significant difference between those with and without hysterectomy in median OS time (59.2 *vs.* 55.5 months) and 5-year OS rate (43.8% *vs.* 40.1%) (Log Rank Mantel-Cox, p=0.340, Figure 3D).

Discussion

To the best of our knowledge, the present study is the largest one involving with clinicopathologic analysis and surgical management for CROM patients. Since clinical features and radiography do not adequately distinguish CROMs from primary ovarian tumors, the CROM cases recruited in our study were confirmed by histopathological diagnosis using resected tumors in the surgeries.

The exact mechanism of CROM is still unclear. What is well known is that colorectal cancer may metastasize to the ovaries via several routes, such as transcoelomic spread, hematogenous metastases, lymphatic spread, and direct extension [12]. In the present study, all primary CRCs were stage T3 or T4, predominantly T4 tumors (88.67%) and 97 (43.7%) patients had developed peritoneal

Table 2: Univariate Analysis for Overall Survival in the all patients and in the R0 resection group.

Factors	All patients			R0 resection group		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (≤ 50 *vs.* >50)	0.983	0.681-1.418	0.926	1.073	0.566-2.033	0.829
Chrolonogy (Synchronous *vs.* Metachronous)	0.837	0.578-1.213	0.348	0.765	0.402-1.457	0.415
Location of CRC (Left colon *vs.* rectum)	0.942	0.588-1.508	0.803	0.727	0.359-1.475	0.377
Location of CRC (right colon *vs.* rectum)	0.876	0.549-1.397	0.578	0.683	0.309-1.508	0.345
T stage (T3 *vs.* T4)	0.835	0.362-1.927	0.672	0.836	0.198-3.534	0.807
Lymph node involvement (- *vs.* +)	0.969	0.566-1.66	0.909	1.278	0.512-3.188	0.6
Hysterectomy (yes *vs.* no)	0.596	0.408-0.87	0.007	0.749	0.406-1.383	0.356
Ovarian involvement (bilateral *vs.* unilateral)	1.098	0.762-1.584	0.616	1.09	0.570-2.082	0.795
oophorectomy (bilateral *vs.* unilateral)	0.73	0.484-1.103	0.135	0.964	0.491-1.891	0.914
Pathology of ovarian (Adenocarcinoma *vs.* Mucinous adenocarcinoma)	1.069	0.698-1.639	0.759	1.018	0.469-2.210	0.963
Ovarian size (≤ 10cm *vs.* >10cm)	0.976	0.657-1.450	0.904	1.713	0.823-3.567	0.15
Combined extrovaian metastases (yes *vs.* no)	2.981	1.859-4.780	0	1.671	0.901-3.099	0.103
Residual tumor classification (R0 *vs.* R1/2)	0.296	0.200-0.438	0			

Table 3: Multivariate analysis for Overall Survival in the all patients.

Factors	HR	95% CI	P-value
Hysterectomy (yes *vs.* no)	0.501	0.336-0.748	0.001
Combined extrovaian metastases (yes *vs.* no)	2.027	1.079-3.810	0.028
Residual tumor classification (R0 *vs.* R1/2)	0.427	0.257-0.709	0.001

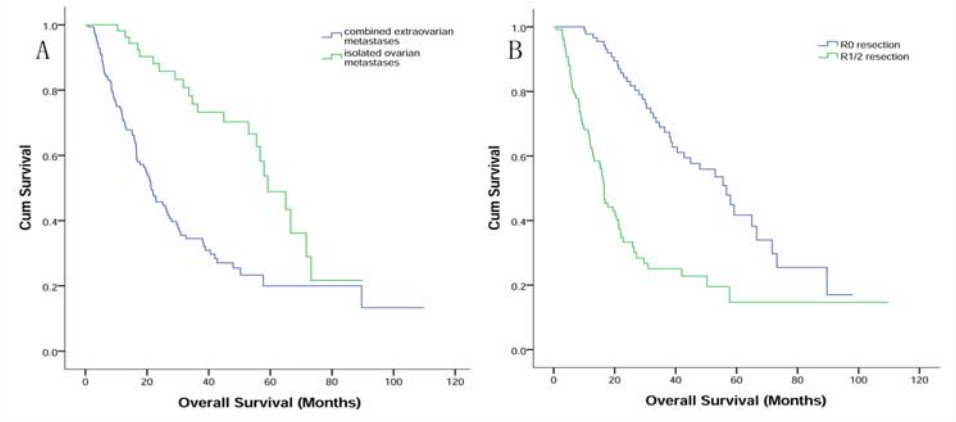

Figure 2: Kaplan-Meier survival curves for Overall Survival (OS) according to independent predictor in all 222 patients. A, Isolated ovarian metastases was associated with improved OS after oophorectomy (p=0.028). B, R0 resection was associated with better OS (p=0.001).

dissemination, which is consistent with the findings of the previous study [11]. This suggests that peritoneal dissemination is highly likely a major route leading to the seeding of the tumor cells in the ovary and consequently results in ovarian metastases.

Ganesh et al., [14] reported a median survival time of 39.6 months in isolated ovarian metastases group and 23.0 months in extra-ovarian metastases group. Similarly, our study revealed a good prognosis in patients with isolated ovarian metastases (n=57) and those with extra-ovarian metastases confined to the pelvic region.

According to Fujiwara et al., [1] the patients who underwent R0 resection or R1/2 resection had a significantly different median survival time (60.5 months *vs.* 13.5 months) and 5-year OS rate (60.6% *vs.* 0%). In the study by McCormick et al., [7] optimal cytoreduction achieved a prolonged progression-free survival and a higher OS rate in patients with localized ovarian metastases or widespread metastases from colon cancers, suggesting that aggressive resection for CROM patients can improve prognosis. In our study, the R0 resection population (n=95) achieved a longer median survival time (56.7 months)and a better 5-year OS rate (41.7%) than the R1/2 resection sub-group (n=127; 16.5 months; 14.7%), indicating that complete resection can contribute to a prolonged survival time. These findings are also consistent with the results of the previous studies [1,4,5,7,8,14].

There are studies reporting ovarian metastases in the preserved ovary after unilateral oophorectomy [1,15]. In the present study, R0 resection patients under bilateral oophorectomy or unilateral oophorectomy for unilateral ovarian metastases showed no significant difference in the survival time. As has mentioned above, 3 out of the 22 patients (13.6%) who underwent unilateral oophorectomy developed metastases in the other ovary. While microscopic ovarian

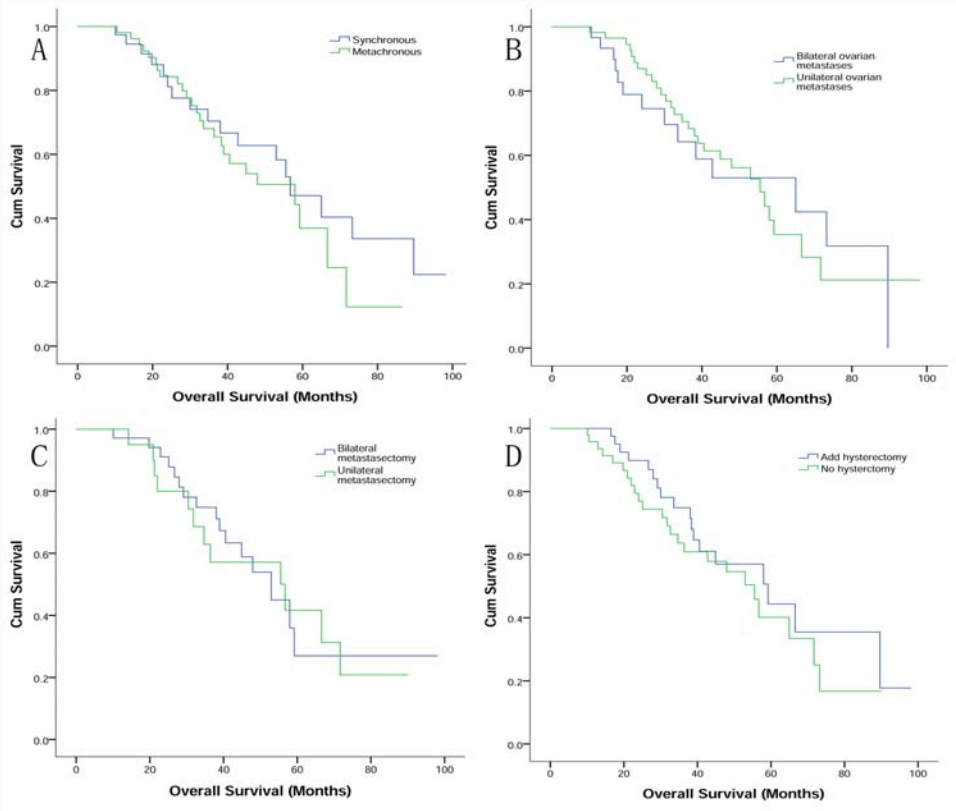

Figure 3: Kaplan-Meier survival curves for Overall Survival (OS) in the R0 resection patients. A: The difference in the OS rate between the synchronous and metachronous groups was not significant (p=0.415). B: Bilateral ovarian metastases was not associated with poor OS (P=0.795). C: Bilateral metastasectomy did not prolong the OS in the R0 group of unilateral ovarian metastases (p=0.967). D: Hysterectomy was not associated with better OS in the R0 resection group without uterine metastases (p=0.340).

metastases were not detected before and during the surgeries. So meticulous preoperative ovary imaging as well as computed tomography scanning and tumor marker assays in regular follow-ups turns out to be extremely critical. As a new finding that was not previously reported, our study found no significant difference in the survival time between bilateral oophorectomy alone and bilateral oophorectomy with hysterectomy for R0 resection patients without uterine invasion. Therefore, for the patients without bilateral ovarian or uterine metastases, we do not suggest a bilateral oophorectomy or hysterectomy due to the negative psychological and physiological impacts of these procedures, such as the loss of fertility, as well as the potential risk of surgical menopause, osteoporosis and ischemic heart diseases. Moreover, avoiding oophorectomy or hysterectomy is beneficial to the patients by a shortened operation time and minimized intraoperative hemorrhage and ureteral injury.

In this study, there are also some results inconsistent with those of previous studies. According to recent studies, patients with unilateral ovarian metastasis had a longer progression-free survival and overall survival time than those with bilateral metastases [2,4,16]. Other studies reported a longer progression-free survival and overall survival time in metachronous metastases as compared to synchronous metastases [15,17]. These differences may be caused by sample bias, as the analysis performed in our study was based on R0 resection sub-group, whereas the previous studies were on patients who underwent either R0 or R1/2 resection.

Limitations in this study include a retrospective nature as well as the information collection from a single institution. Besides, some of the patients were lost to the follow-ups. In addition, all the patients included in this study had undergone the surgeries, so there was no chance to compare these patients with those who did not received surgeries.

Conclusion

In conclusion, this study suggests that patients with colorectal cancer in the T4 stage are more prone to ovarian metastasis. R0 resection is highly recommended for resectable tumors due to the longer survival time and higher survival rate in comparison to R1/2 resection. Moreover, unilateral oophorectomy should be prioritized after adequate assessment for younger women with unilateral ovarian metastases to preserve their ovarian function as much as possible, and hysterectomy is not recommended for R0 resection patients without uterine metastasis. These findings in our study can provide a reference for gynecologists in formulating treatment strategy and selecting surgical procedures.

Acknowledgment

This study was supported by grants from the National Natural Science Foundation of China (No.81472620); Shanghai Science and Technology Planning Fund (No.13140902100); Shanghai Combination Study Project for Major Disease (No.2014ZYJB0101); and Shanghai Health and Family Planning Commission (No. JGY1404).

Author Contribution

All authors did significantly contribute to the conception or

design of the work and the acquisition, analysis, and interpretation of data. All authors critically revised the final manuscript. All authors approved the final version of the manuscript to be published. All authors agree to be accountable for all aspects of the work.

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