Original Article

Clinical Characteristics and Outcomes of Ovarian Metastasis from Colorectal Cancer: A Single-center Experience

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Key Words
Colorectal cancer;
Ovarian metastasis;
Prognosis

Purpose. The current study aimed to analyze the characteristics and outcomes of patients with colorectal cancer and ovarian metastasis.
Methods. We reviewed the data of all patients with confirmed ovarian metastasis from colorectal cancer who underwent surgical resection at the Mackay Memorial Hospital between January 2007 and December 2020. A total of 28 patients were enrolled in the study: 17 with synchronous metastases and 11 with metachronous ovarian metastases. The patients' clinical characteristics and prognoses were analyzed.
Results. The mean age at diagnosis of the patients with ovarian metastases was 52.1 years. The average overall survival time after surgery was 31.3 ± 9.48 months. The percentage of patients with synchronous and metachronous metastases was 61% and 39%, respectively. The average detection interval of the metachronous metastases was 22.3 months. Slightly elevated serum carcinoembryonic antigen and cancer antigen 125 levels (6.57 ng/mL and 19.14 U/mL, respectively) were observed in the metachronous group. Optimal resection (R0) was achieved in 17 (61%) patients. The peritoneum (43%) was the most common site of concurrent metastasis, followed by the liver (21%). Compared with R1 and R2 resections, patients who underwent R0 resections had significantly improved overall survival ($p = 0.023$).
Conclusions. Metastatic ovarian tumors in the colorectal region are rare and have poor survival outcomes. The levels of carcinoembryonic antigen or cancer antigen 125 may not be very accurate in demonstrating the presence of metachronous ovarian metastasis. Although the prognosis is not optimistic, curative resection can significantly improve patients' overall survival.

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Colorectal cancer (CRC) is one of the most common malignancies worldwide.[1] In Taiwan, CRC remains the most common cancer in men and the second most common cancer in women.[2] At the time of diagnosis, approximately 20% of CRC patients have already developed metastatic disease.[3] The most common metastatic site for patients with CRC is the liver, followed by the lungs.[4,5] The incidence of ovarian metastasis from colorectal cancer is relatively rare and was reported to be 3.7-7.4% in a previous study; however, it remains one of the major cause of death in female patients.[6,7]

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The prognosis for patients with ovarian metastasis (OM) remains poor. This may be associated with the diagnostic challenges it presents due to its rarity and lack of sensitivity to chemotherapy.[8] Unfortunately, the treatment options for OM remain controversial. Many studies have discussed the value of surgery, but the advantages of surgery have not yet been well defined or proven yet.[9]

In this retrospective study, we aimed to analyze the characteristics of patients with CRC who presented with OM. Moreover, we investigated the importance and survival outcomes of surgical resection for the treatment of ovarian metastases originating from CRC.

Materials and Methods

The current study reviewed the data of all patients with histologically confirmed ovarian metastasis from CRC who underwent surgical resection at Mackay Memorial Hospital between January 2007 and December 2020. Follow-up data were collected until September 2021. This study was approved and performed in accordance with the standards of the Ethical Committee of the MacKay Memorial Hospital.

There were total 62 patients who were diagnosed with CRC-OM during the study period. Patients who did not undergo surgery for primary tumor lesions or ovarian metastatic lesions were excluded from the study. Patients lost to follow-up at our hospital were also excluded. Finally, 28 patients were enrolled in the study: 17 patients with synchronous ovarian metastases and 11 patients with metachronous ovarian metastatic lesions.

Synchronous metastases were defined as ovarian metastases detected at the same time as CRC within three months. Metachronous metastases were defined as ovarian metastases detected at least 3 months after the diagnosis of CRC. Patient information including age, site of the primary colorectal tumor, staging of the colorectal cancer, serum carcinoembryonic antigen (CEA) level, cancer antigen 125 (CA-125) level, type of surgery performed, degree of the residual tumor, lymph-vascular-perineural invasion, and site of concurrent metastasis were collected. Overall survival (OS) was evaluated based on the initial diagnosis of CRC-OM. Clinicopathological characteristics and prognostic conditions were retrospectively analyzed.

Qualitative parameters were compared using the chi-square test. Overall survival was analyzed using the Kaplan-Meier method, and differences in survival between groups were compared using the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazard regression models. Significant factors in Cox's analysis were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The Statistical Package for the Social Sciences software for Windows (version 22.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Statistical significance was set at $p < 0.05$.

Results

Twenty-eight patients with CRC-OM were enrolled in the study. Synchronous metastases were detected in 17 cases and metachronous metastases were detected in 11 cases. The median follow-up time was 32 months (range: 1-101 months). The mean age at diagnosis of the patients with ovarian metastases was 52.1 years (range: 33-81 years, SD: 14.89). More than half of the primary tumors (n = 16, 57%) originated in the left colon. The percentage of patients with synchronous and metachronous metastases was 61% (n = 17) and 39% (n = 11), respectively. The average detection interval of the metachronous metastases was 22.3 months (range, 11-39 months). The preoperative median CEA and CA-125 levels in all of the patients were 23.47 ng/mL and 42.39 U/mL, respectively. In the synchronous group, the median CEA and CA-125 levels were significantly elevated at 73.95 ng/mL and 147 U/mL. On the contrary, only slightly elevated CEA and CA-125 levels (6.57 ng/mL and 19.14 U/mL, respectively) were observed in the metachronous group. Most of our patients had T3 or T4 tumors, only one patient presented with T2 tumors. Approximately 85.7% (n = 24) of patients had lymph node metastases. Most patients presented with vascular, lymphatic, and perineural invasion; 20 (71%) patients presented with vascular invasion, 24 (86%) presented

with lymphatic invasion, and 18 (64%) presented with perineural invasion. Only two patients did not present with vascular, lymphatic, or perineural invasion.

More than half of our patients (n = 17, 61%) achieved optimal resection (R0) and 11 patients achieved suboptimal resections (R1 or R2). Eleven (39%) patients presented with metastasis to the ovary alone, and seventeen (61%) had metastasis to the ovary and other sites, including the peritoneum, liver, and lungs. The peritoneum (49%) was the most common site of concurrent metastasis, followed by the liver (24%). Eight patients in the metachronous group received preoperative chemotherapy; the regimens were fluorouracil-based and included oxaliplatin or irinotecan. As analyzed by the Kaplan-Meier method, the mean overall survival time after surgery was 31.3 ± 9.48 months (95% confidence interval: 21.8-40.8). In the synchronous group, the average was 30.6 ± 13.9 months (95% confidence interval: 16.7-44.5), and this was 32.3 ± 11.7 months (95% confidence interval: 16.7-44.5) in the metachronous group (Table 1).

The univariate analysis showed that only ovarian

Table 1. Clinical and pathologic characteristics

	Number of participants (N = 28)	Synchronous metastasis (N = 17) (61%)	Metachronous metastasis (N = 11) (39%)
Mean age	52.1 (33-81)	51.3	53.3
Tumor location			
Colon, right side	8	5	3
Colon, left side	16	8	8
Rectum	4	4	0
Pre-op biomarker			
Median CEA level (< 5 ng/mL)	23.47 (0.69-1200)	73.95 (8.17-1200)	6.57 (0.69-111.88)
Median CA-125 level (< 35 U/mL)	42.39 (11.53-1346)	147 (37.82-1346)	19.14 (11.53-20.2)
T stage			
T1	0		
T2	1		1
T3	15	7	8
T4	12	10	2
N stage			
N0	4	3	1
N1	13	4	9
N2	11	10	1
Pathology			
MD adenocarcinoma	19	10	9
PD adenocarcinoma	2	1	1
Mucinous/Signet-ring cell	7 (5/2)	6 (4/2)	1
Oophorectomy for ovarian tumor			
Unilateral	15	7	8
Bilateral	13	10	3
Degree of residual tumor			
R0	17	7	8
R1 or R2	11	10	3
Extent of metastasis			
Ovary alone	11	6	5
Ovary +1 site	10	6	4
Ovary + ≥ 2 sites	7	5	2
Site of concurrent metastasis			
Liver	6	4	2
Lung	2	1	1
Uterus	5	4	1
Peritoneum	12	7	5
Preoperative chemotherapy	8	0	8
Mean survival time (M)	31.3	30.65	32.27

metastases and the degree of the residual tumor were significantly associated with longer OS times (Table 2). Similar results were seen in the multivariate analysis, with ovarian metastases alone (55 vs. 17 months; hazard ratio [HR]: 0.212; $p = 0.008$) and the degree of the residual tumor (R0 resection compared with R1 or R2 resection) being significantly correlated with improved overall survival (55 vs. 12 months; hazard ratio [HR]: 0.313; $p = 0.023$) (Fig. 1 and 2).

Discussion

Metastatic ovarian tumors account for approximately 21.5% of all malignant ovarian tumors; 3.7-7.4% of the cases are metastases from colorectal cancer,[6,7,10] and these cases are frequently diagnostically confused with primary ovarian cancer.[11,12] However, the pathway or route by which CRC metastasizes to the ovary remains unclear. Graffner et al.[6] and Birnkrant et al.[13] hypothesized that there is no lymph flow between the colon and ovaries. Both hematogenous and disseminated peritoneal metastases present possible metastatic pathways. This might explain why almost half of the patients in our study presented with peritoneal metastasis or carcinomatosis at the time of ovarian metastasis diagnosis. In our study, 47% (8/17) of the patients were first viewed as having primary

Table 2. Result of the univariate and multivariate analyses of overall survival

	Univariate analysis (p-value)	Multivariate analysis (p-value [95% CI], hazard ratio)
Tumor invade staging (T3 vs. T4)	0.250	
Lymph node status (N0 vs. N1-2)	0.678	
Degree of residual tumor (R0 vs. R1 or R2)	0.012	0.023 [0.115-0.852], 0.313
Vascular invasion	0.096	
Lymphatic invasion	0.330	
Perineural invasion	0.703	
Oophorectomy (unilateral vs. bilateral)	0.801	
Number of metastatic sites (ovary alone vs. ovary +1-2 sites)	0.003	0.008 [0.068-0.662], 0.212

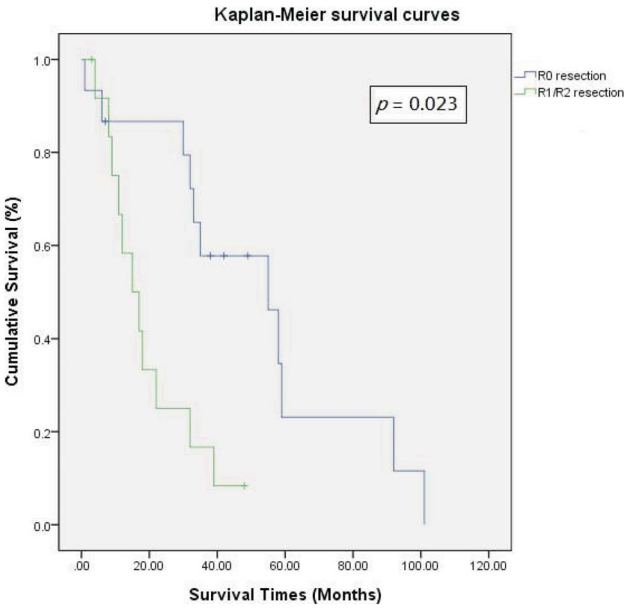

Fig. 1. Overall survival curves of patients with ovarian metastasis from colorectal cancer. Kaplan-Meier survival curves showing the survival benefit of complete cytoreduction (R0 resection) ($p = 0.023$).

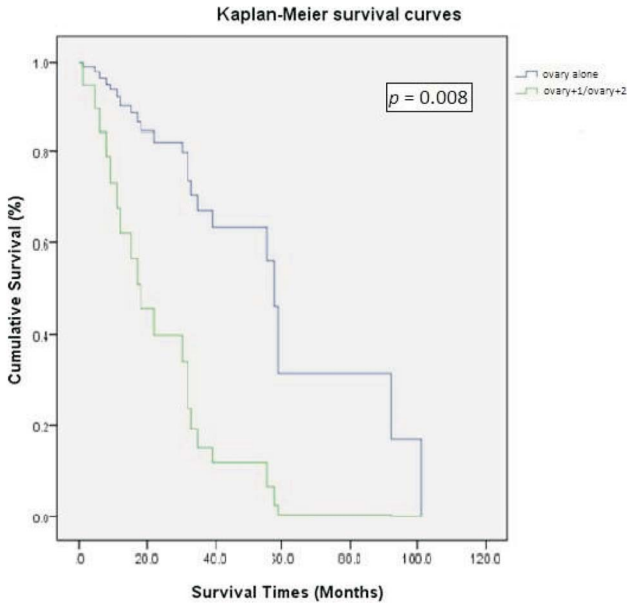

Fig. 2. Kaplan-Meier survival curves showing the survival benefits for patients with only ovarian metastasis ($p = 0.008$).

ovarian tumors, and most of them were found to have colon or rectal cancer during the operation. Even with improvements in our examination tools and techniques, distinguishing between primary and metastatic ovarian cancer remains difficult and challenging.

Tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) have been studied to improve the preoperative diagnosis of primary ovarian cancer and ovarian metastasis. In a previous study by Sørensen et al., a cutoff value below 25 from the CA-125/CEA ratio demonstrated high accuracy in identifying ovarian metastasis over primary ovarian malignancy.[14] Most of the patients in our study presented with a CA-125/CEA ratio below 25, except for two patients. Based on these results, we suggest that a CA-125/CEA ratio below 25 can be indicative of ovarian tumors originating from the colorectal regions as opposed to from primary ovarian cancer.

In addition, the tumor marker CEA has been widely used as an indicator of progression, recurrence, or metastasis in patients with CRC who have received treatment.[15] Similar to CEA, CA-125 has been viewed as a marker that may affect ovarian status. In our study, significantly elevated CEA and CA-125 levels were observed in patients with synchronous ovarian metastasis. The median CEA level was 23.47 ng/mL, and the median CA-125 level was 42.39 U/mL in these patients. In contrast, only slightly elevated CEA levels were observed in the metachronous group (median, 6.57 ng/mL). Moreover, the level of CA-125 in all patients in the metachronous group was within the normal range (median level, 19.14 U/mL). Based on this finding, neither CEA nor CA-125 appears to be an ideal tool for detecting the presence of metachronous ovarian metastasis. Other imaging methods such as ultrasound examination, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) should be considered as additional follow-up examinations.

In our study, synchronous ovarian metastases were defined as ovarian metastases detected within 3 months of the patient's colorectal cancer diagnosis. Metachronous ovarian metastases were defined as the presence of ovarian metastases three months after the diagnosis of colorectal cancer. Several single-center studies have shown that the incidence rate of synchronous ovarian metastases is 0-9% and that the incidence rate of metachronous ovarian metastases was 0.9-7%.[16,17] Xu et al. found that women younger than 50 years and premenopausal women might have a higher rate of synchronous ovarian metastases.[18] We found a similar trend in our study, in the group with synchronous ovarian metastases, 53% patients were younger than 50 years. Thus, young women who present with CRC should be more aware of ovarian metastases. In a previous study, metachronous ovarian metastases usually occurred within 2 years after CRC surgery.[16,18] Similar results were observed in our study: the average detection interval of the ovarian metastases was 22.3 months. This result suggests that female patients who undergo CRC surgery should be aware of possible ovarian invasion within 2 years in order to detect it early and to receive timely treatment, which may lead to a better prognosis.

In previous studies, synchronous or metachronous ovarian metastases did not affect the prognosis of patients with CRC-OM.[16] However, other studies have suggested that the survival of synchronous metastases is better than that of metachronous metastases.[19] In our study, there is no significant difference in the average overall survival times between the synchronous and metachronous groups (30.6 ± 13.9 months vs. 32.3 ± 11.7 months; $p = 0.407$). Furthermore, there were no significant differences in survival between T staging, N staging, unilateral or bilateral ovarian involvement, lymphovascular invasion, perineural invasion, and cellular histology in our study. In contrast, the number of metastatic sites significantly affected the patients' survival times (55 vs. 17 months; $p = 0.008$). However, due to the small sample size, this result may be based on a selection bias, and larger amounts of data should be collected to identify precise prediction factors that are related to prognosis.

The treatment strategy for ovarian metastasis of CRC remains controversial. In current practice, for potentially resectable metastatic lesions in the liver or lung, an aggressive surgical approach is warranted for both the primary and metastatic sites, which can lead to better patient prognosis.[20] As for the ovarian meta-

stases, Rayson et al. revealed that complete resection for ovarian metastasis was associated with prolonged overall survival.[21] In our study, we found that for both synchronous and metachronous patients, if a complete cytoreductive surgery could be achieved (R0 resection), this was associated with a significant improvement in patient survival compared to in patients in which an incomplete resection was achieved (R1 or R2 resection) (55 vs. 12 months; $p = 0.023$). Therefore, we suggest that patients with ovarian metastases of CRC should undergo aggressive surgical resection for both primary and metastatic lesions in order to achieve better survival outcomes.

This study had several inherent limitations. Due to the retrospective study design, the data were obtained by chart review, and there might be some potential selection bias. For example, there was incomplete follow-up information as well as heterogeneity in the patients, tumors, and treatment-related characteristics. Second, this was a single-center study, with a small sample size. Therefore, these results may not be applicable to other populations. This could also explain why most of our results did not lead to significant differences. It is still necessary to further verify this conclusion in prospective multicenter studies with larger sample sizes and to identify the characteristics of synchronous and metachronous ovarian metastasis of colorectal origin.

Conclusion

Metastatic ovarian tumors in the colorectal cancer patients are rare and have poor survival outcomes. The levels of CEA or CA-125 may not be very accurate in demonstrating the presence of metachronous ovarian metastasis. Although the prognosis is not optimistic, curative resection can significantly improve patients' OS.

Ethical Considerations

Ethical approval to conduct the study was obtained from the ethics review committee of Mackay Memorial Hospital before the commencement of the study.

Conflicts of Interest

The authors declare no conflicts of interest.

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原　著

結直腸癌卵巢轉移的臨床特徵與預後分析：單中心經驗

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介紹　分析大腸直腸癌合併卵巢轉移病人的臨床特徵及預後。

方法　回朔性分析單一醫學中心自 2007 年 1 月至 2020 年 12 月，期間共 28 位女性病患被診斷大腸直腸癌合併有卵巢轉移並接受手術切除被納入研究。

結果　共 28 位病患平均年齡為 52.1 歲，平均術後存活時間為 31.3 個月。其中 17 位 (61%) 病患爲同時性卵巢轉移，另外 11 位 (39%) 為異時性轉移性卵巢轉移。平均發生轉移性卵巢轉移的時間為 22.3 月及術前的 CEA 和 CA-125 分別為 6.57 ng/mL 和 19.14 U/mL。有 17 (61%) 位病患接受治癒性 (R0) 切除。最常見同時合併有轉移的位置依序為腹膜及肝臟。在多變數分析中，治癒性切除相較非治癒性切除有顯著的較好預後及整體存活率 (55 vs. 12 月，$p = 0.023$)。

結論　儘管大腸直腸癌合併卵巢轉移的病人預後較差，且 CEA 和 C-125 也不是一個很好的追蹤卵巢轉移的指標，但我們的研究結果顯示治癒性切除能顯著的提高病人的整體存活率。

關鍵詞　大腸直腸癌、卵巢轉移、預後。