Original Article

Synchronous Ovarian Metastasis from Colorectal Cancer: Characteristics and Long-term Survival Analysis

Chien-En Tang[1]
Kung-Chuan Cheng[1]
Yu-Che Ou[2,3]
Hong-Hwa Chen[1]
Wan-Hsiang Hu[1]
Ko-Chao Lee[1,4]

[1]*Division of Colorectal Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, College of Medicine,*
[2]*Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, College of Medicine, Kaohsiung,*
[3]*Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital Chiayi Branch, Chang Gung University College of Medicine, Chiayi,*
[4]*Department of Information Management & College of Liberal Education, Shu-Te University, Kaohsiung, Taiwan*

Key Words
Colorectal cancer;
Ovarian metastasis;
Synchronous;
Prognosis

Purpose. Ovarian metastasis (OM) occurs in patients with colorectal cancer (CRC). The current study aimed to evaluate the characteristics and prognosis of patients with synchronous OM from CRC and to establish an optimal management plan.

Methods. We performed a single-center retrospective review. From January 2001 to December 2012, 2191 female patients were diagnosed with primary CRC in our institution. The data of 62 patients with synchronous OM who underwent primary tumor resection and oophorectomy were collected for analysis. Then, the patients' clinicopathological characteristics and prognosis were analyzed.

Results. The median age at diagnosis was 50 (range: 26-81) years. The median survival time after surgery was 14 (95% confidence interval: 12-25) months. None of the patients presented with less than T3 tumor, and almost all patients had an N-positive tumor. In total, 53 (86%) patients had moderately differentiated adenocarcinoma; 2 (3%), poorly differentiated adenocarcinoma; and 7 (11%), mucinous adenocarcinoma. Moreover, 35 (56%) patients experienced bilateral ovarian involvement. Curative resection (R0) was achieved in 15 (24%) patients. The peritoneum (45%) was the most common concurrent metastatic site, followed by the liver (42%) and retroperitoneal lymph nodes (16%). Compared with R1 or R2 resection, R0 resection was associated with a better prognosis (38 vs. 12 months; hazard ratio: 0.3; $p = 0.0165$) in a multivariate analysis.

Conclusions. Although OM from CRC is associated with poor outcomes, curative resection may significantly improve overall survival.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2021;32:27-32*]

Colorectal cancer (CRC) is a common disease worldwide. More than 20% of patients are diagnosed with stage IV CRC or metastatic disease, and they have a poor 5-year overall survival rate (less than 14%).[1,2] The common sites of distant metastasis are the liver and lung.[3] In contrast, the ovary is a relatively rare metastatic site for colorectal cancer, with an incidence rate approximately 1%-14%.[4-6] Diagnostic challenges caused by its rarity and relative chemoresistance, are associated with poor prognosis in patients with ovarian metastasis (OM).[7,8] In previous studies, synchronous OM was considered an independent risk factor associated with poor survival,[9,10] and most patients died within 1 year after the diagnosis of OM.

Received: July 10, 2020. Accepted: August 25, 2020.
Correspondence to: Dr. Ko-Chao Lee, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 83301, Taiwan. Tel: 886-7-731-7123; Fax: 886-7-731-8762; E-mail: kmch4329@gmail.com

Therefore, it has been considered a late-stage disease.[11] OM from CRC is correlated with an extremely poor outcome.[11] Furthermore, the optimal treatment for OM is still controversial. The current retrospective study aimed to analyze the characteristics and outcomes of patients with colorectal cancer who presented with synchronous OM. Moreover, the prognostic factors of the disease were investigated.

Materials and Methods

The current study was approved by the institutional review board of Chang Gung Memorial Hospital. We reviewed the data of all patients with histologically confirmed synchronous ovarian metastasis from CRC who underwent surgical resection at our institution between January 2001 and December 2012.

In total, 2191 female patients with primary CRC were diagnosed during the study period. Of them, 65 had ovarian tumor at the time of initial diagnosis. Then, 62 patients with synchronous OM who underwent primary tumor resection and oophorectomy were included in the analysis. Three patients, including one with a pathological report showing endometrioid ovarian adenocarcinoma and two who did not undergo primary tumor resection, were excluded. Patient information, including age, site of colorectal primary tumor, staging of colorectal cancer, ovarian tumor size, serum carcinoembryonic antigen level, type of surgery performed, degree of residual tumor and extent and site of concurrent metastasis, was collected and analyzed. Survival was defined as time from diagnosis to death or the last follow-up. To evaluate resection margin, we used the residual classification by the American Joint Committee on Cancer Staging Manual, 7th edition. R0 resection indicated a microscopically negative margin, suggesting that there was no residual tumor. R1 and R2 resection indicated microscopic and macroscopic residual tumors.

We used the Statistical Package for the Social Sciences software for Windows version 20.0 (IMB Corp., Armonk, NY, the USA) for statistical analysis. Qualitative parameters were compared using the chi-square test. Overall survival was evaluated using the Kaplan-Meier method, and the differences in survival between groups were assessed using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazard models. p values less than 0.05 were considered statistically significant.

Results

There were 2191 female patients diagnosed with primary CRC during the study period. Of them, 62 (2.82%) with synchronous OM who underwent primary tumor resection and oophorectomy were included in the analysis (Table 1). The median age at diagnosis

Table 1. Demographic characteristics of the patients

	Number of participants (%) N = 62
Median age	50.2 (46.7-53.7)
Tumor location	
Right side of the colon	13
Left side of the colon	28
Rectum	21
T stage	
T1	0
T2	0
T3	1
T4	61
N stage	
N0	1
N1	36
N2	25
Pathology	
MD adenocarcinoma	53
PD adenocarcinoma	2
Mucinous adenocarcinoma	7
Oophorectomy for ovarian tumor	
Bilateral	35
Unilateral	27
Degree of residual tumor	
R0	15
R1 or R2	47
Extent of metastasis	
Ovary alone	9
Ovary + 1 site	15
Ovary + ≥ 2 sites	38
Site of concurrent metastasis	
Liver	26
Lung	4
Peritoneum	28
Retroperitoneal lymph node	10
Preoperative chemotherapy	0

MD, moderate differentiated; PD, poorly differentiated.

was 50 (range: 26-81) years. The median survival time after surgery was 14 (95% confidence interval: 12-25) months. None of the patients presented with less than T3 tumor, and 61 had T4 tumor. Approximately 98.4% (n = 61), had lymph node metastasis. Moreover, 53 (86%) patients had moderately differentiated adenocarcinoma; 2 (3%), poorly differentiated adenocarcinoma; and 7 (11%), mucinous adenocarcinoma.

In total, 26 patients with OM underwent unilateral salpingo-oophorectomy; 22, bilateral salpingo-oophorectomy plus hysterectomy; 13, bilateral salpingo-oophorectomy; and 1, unilateral salpingo-oophorectomy plus hysterectomy. Bilateral ovarian involvement was observed in 35 (56%) patients. Optimal resection (R0) was achieved only in 15 (24%) patients and sub-optimal resection (R1 or R2) in 47 patients. Nine (14.5%) patients presented with metastasis in the ovary alone, and 38 (61.3%) with metastasis in the ovary and in more than two sites, including the peritoneum, liver, retroperitoneal lymph nodes, lung, and brain. The peritoneum (45%) is the most common concurrent metastatic site, followed by the liver (42%) and retroperitoneal lymph nodes (16%). Fifty (81.9%) patients received chemotherapy after surgery. All postoperative chemotherapeutic regimens were fluorouracil-based, which includes oxaliplatin or irinotecan. In total, 10 and 16 patients received bevacizumab and cetuximab, respectively.

Degree of residual tumor, concurrent liver metastasis, peritoneal carcinomatosis and numbers of concurrent metastasis sites were significantly associated with overall survival in a univariate analysis (Table 2). However, in a multivariate analysis, only degree of residual tumor (R0 resection compared with R1 or R2 resection) was significantly correlated with improved overall survival (38 vs. 12 months; hazard ratio [HR]: 0.3; $p = 0.0165$) (Fig. 1).

Discussion

CRC with distant OM is rare disease with an inci-

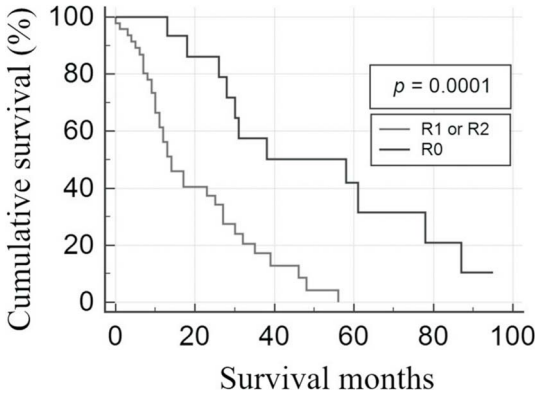

Fig. 1. Overall survival curves of patients with synchronous ovarian metastasis from colorectal cancer. Kaplan-Meier survival curves showing the survival benefit of complete cytoreduction (R0 resection) ($p = 0.0001$).

Table 2. Univariate and multivariate analysis of overall survival in patients with synchronous ovarian metastasis from colorectal cancer

	Univariate analysis (p value)	Multivariate analysis (p value [95% CI], hazard ratio)
Age (< 50 vs. ≥ 50 years)	0.9066	
Tumor location (rectum vs. colon)	0.1167	
Lymph node (N0-1 vs. N2)	0.1595	
Degree of residual tumor (R0 vs. R1 or R2)	0.001	0.0165 [0.1114-0.8020], 0.2989
Tumor deposit	0.2452	
Lymphovascular invasion	0.5252	
Perineural invasion	0.4792	
Oophorectomy (unilateral vs. bilateral)	0.2225	
Liver metastasis	0.0264	0.8829 [0.5254-2.1130]
Lung metastasis	0.9444	
Peritoneal seeding	0.0023	0.20006 [0.7820-3.2267]
Retroperitoneal LN metastasis	0.0626	
Numbers of concurrent metastasis sites (1 or 2 vs. ≥ 3)	0.0038	0.5557 [0.3665-1.7154)

dence rate of 1%-14%, according to previous studies.[4-6] However, it is responsible for the most frequent diagnostic confusions with primary ovarian cancer.[12,13] In our study, only nine patients complained of bloody stool, which is typically an early sign of CRC. Therefore, not all patients with ovarian tumor underwent preoperative colon screening, including barium enema or colonoscopy. In a previous study by Lee et al., in patients with a cancer antigen-125-to-carcinoembryonic antigen ratio less than 25, a diagnosis of OM from CRC should be considered.[8]

The possible mechanisms underlying the development of OM are as follows: lymphatic, hematogenous, and transcoelomic spread. Lymphatic spread is considered the main mechanism of metastasis.[14] That there are large amount of lymphatic tissues and vessels around the ovary and mesosalpinx. This finding might explain why almost all patients had lymph node metastasis in our study. Moreover, patients with OM were younger and mainly premenopausal compared with those who had primary ovarian cancer. Meanwhile, the functioning ovary was at risk of metastatic disease due to its rich blood supply, indicating hematogenous spread.[15] Honore et al. have reported that synchronous ovarian metastasis is a risk factor of peritoneal carcinomatosis.[16] The coincidence of ovarian metastasis and peritoneal carcinomatosis indicated the mechanism of transcoelomic spread. Similarly, 61 (98.4%) patients presented with T4 tumor, and 28 (45.2%) patients had concurrent peritoneal carcinomatosis in our study.

The optimal treatment strategy for synchronous OM from CRC remains controversial. The Japanese guidelines for colorectal cancer treatment showed that surgery is indicated for metastatic lesions if the primary colorectal and metastatic lesions can be completely resect and if the patients can tolerate surgical intervention.[17] Complete surgical resection of metastatic tumors is currently considered a curative treatment for CRC patients with liver metastasis.[18] Rayson et al. revealed that complete metastasectomy for ovarian metastasis was associated with prolonged overall survival.[19] In our study, complete cytoreductive surgery (CRS) (R0 resection) was significantly beneficial for overall survival compared with incomplete cytoreductive surgery (R1, R2 resection) (38 vs. 12 months; HR: 0.3; $p = 0.0165$). The survival benefit of complete metastasectomy was similar to that in previous studies. Based on these findings, if feasible, complete metastasectomy is recommended for synchronous OM in CRC patients.

Despite the limited supporting data, bilateral salpingo-oophorectomy should be considered in OM patients because the incidence of bilateral ovarian involvement was high (31%-75%), and bilateral ovary was considered to have a similar risk of metastatic involvement.[10,19,20] Eveno et al. reported a high incidence of ovarian metastasis in patients with colorectal peritoneal carcinomatosis. Moreover, bilateral salpingo-oophorectomy with CRS in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) was recommended for patients with concurrent ovarian metastasis and peritoneal carcinomatosis.[21] Kuijpers et al. obtained a similar conclusion showing that CRS-HIPEC is associated with better overall survival in patients with concurrent ovarian metastasis and peritoneal carcinomatosis.[22] Further investigations should be conducted to further identify groups who may have benefit from an aggressive surgical approach, including CRS-HIPEC.

This study had several limitations. First, its retrospective design was based on chart review, which might have resulted in an inherent selection bias. Second, patients with OM but without significant symptoms might not have received treatment nor were enrolled in the study. In addition, the small sample size, was small due to the rarity of OM from primary CRC. Moreover, the surgeon's experience and patients' desire to undergo aggressive surgery due to its potential benefits might have resulted in selection bias. Finally, these results were obtained from a study population at a single medical center; and hence, they may not be generalized to other populations.

Conclusions

Ovarian metastasis from colorectal cancer is associated with poor outcomes. However, if feasible, curative resection can significantly improve overall sur-

vival. We recommended extensive resection to achieve R0 resection for better overall survival and clinical outcome.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683-91.
2. Lee-Ying R, Bernard B, Gresham G, et al. A comparison of survival by site of metastatic resection in metastatic colorectal cancer. *Clin Colorectal Cancer* 2017;16:e23-8.
3. Qiu M, Hu J, Yang D, Cosgrove DP, Xu R. Pattern of distant metastases in colorectal cancer: a SEER based study. *Oncotarget* 2015;6:38658-66.
4. Segelman J, Floter-Radestad A, Hellborg H, Sjovall A, Martling A. Epidemiology and prognosis of ovarian metastases in colorectal cancer. *Br J Surg* 2010;97:1704-9.
5. Blamey S, McDermott F, Pihl E, Price AB, Milne BJ, Hughes E. Ovarian involvement in adenocarcinoma of the colon and rectum. *Surg Gynecol Obstet* 1981;153:42-4.
6. Ojo J, De Silva S, Han E, et al. Krukenberg tumors from colorectal cancer: presentation, treatment and outcomes. *Am Surg* 2011;77:1381-5.
7. Lewis MR, Deavers MT, Silva EG, Malpica A. Ovarian involvement by metastatic colorectal adenocarcinoma: still a diagnostic challenge. *Am J Surg Pathol* 2006;30:177-84.
8. Lee KC, Lin H, Chang Chien CC, et al. Difficulty in diagnosis and different prognoses between colorectal cancer with ovarian metastasis and advanced ovarian cancer: an empirical study of different surgical adoptions. *Taiwan J Obstet Gynecol* 2017;56:62-7.
9. Omranipour R, Abasahl A. Ovarian metastases in colorectal cancer. *Int J Gynecol Cancer* 2009;19:1524-8.
10. Wu F, Zhao X, Mi B, et al. Clinical characteristics and prognostic analysis of Krukenberg tumor. *Mol Clin Oncol* 2015; 3:1323-8.
11. Fujiwara A, Noura S, Ohue M, et al. Significance of the resection of ovarian metastasis from colorectal cancers. *J Surg Oncol* 2010;102:582-7.
12. Young RH. From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary: part I. Historical perspective, general principles, mucinous tumors including the krukenberg tumor. *Adv Anat Pathol* 2006;13:205-27.
13. Young RH. From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary. Part II. *Adv Anat Pathol* 2007;14:149-77.
14. Qiu L, Yang T, Shan XH, Hu MB, Li Y. Metastatic factors for Krukenberg tumor: a clinical study on 102 cases. *Med Oncol* 2011;28:1514-9.
15. La Fianza A, Alberici E, Pistorio A, Generoso P. Differential diagnosis of Krukenberg tumors using multivariate analysis. *Tumori* 2002;88:284-7.
16. Honore C, Goere D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. *Ann Surg Oncol* 2013;20:183-92.
17. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 2020; 25:1-42.
18. Siebenhuner AR, Guller U, Warschkow R. Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases. *BMC Cancer* 2020;20:246.
19. Rayson D, Bouttell E, Whiston F, et al. Outcome after ovarian/adnexal metastectomy in metastatic colorectal carcinoma. *J Surg Oncol* 2000;75:186-92.
20. Erroi F, Scarpa M, Angriman I, et al. Ovarian metastasis from colorectal cancer: prognostic value of radical oophorectomy. *J Surg Oncol* 2007;96:113-7.
21. Eveno C, Goere D, Dartigues P, et al. Ovarian metastasis is associated with retroperitoneal lymph node relapses in women treated for colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2013;20:491-6.
22. Kuijpers AM, Mehta AM, Aalbers AG, et al. Treatment of ovarian metastases of colorectal and appendiceal carcinoma in the era of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* 2014;40:937-42.

原　著

同時性大腸直腸癌卵巢轉移臨床表現及術後存活分析

唐健恩[1]　鄭功全[1]　歐育哲[2,3]　陳鴻華[1]　胡萬祥[1]　李克釗[1,4]

[1]高雄長庚紀念醫院　外科部　大腸直腸外科

[2]高雄長庚紀念醫院　婦產部

[3]嘉義長庚紀念醫院　婦產科

[4]樹德科大　資訊管理系　通識教育學院

目的　評估大腸直腸癌合併同時性卵巢轉移的病人的臨床表現及不同治療方式預後。

方法　回朔性分析單一醫學中心自 2001 年 1 月至 2012 年 12 月共 2192 名被診斷大腸直腸癌之女性患者，共 62 位病患合併有同時性卵巢轉移併接受手術切除被納入分析。

結果　病患族群平均年齡為 50 歲，平均術後存活時間為 14 個月 (95% 信賴區間：12-25 月)。所有病患腫瘤侵犯程度均為 T3 以上，且幾乎都有淋巴結轉移。有 15 (24%) 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，肝臟及後腹腔淋巴結。在多變數分析中，治癒性切除與非治癒性切除相較之下有較佳的預後及總存活期 (38 vs. 12 月，風險比率 0.3，$p = 0.0165$)。

結論　儘管大腸直腸癌合併卵巢轉移預後差，但我們的研究結果顯示治癒性切除對於總存活期有顯著的幫助。

關鍵詞　大腸直腸癌、卵巢轉移、同時性、預後。