***Original Article***

# Characteristics and Prognostic Factors of Ovarian Metastasis from Colorectal Cancer

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***Key Words***
Colorectal cancer;
Ovarian metastasis;
Synchronous;
Metachronous

***Abbreviations***
CRC: colorectal cancer;
OM: ovarian metastasis;
OMS: ovarian metastasis survival;
LAP: lymphadenopathy

***Purpose.*** Ovarian metastasis (OM) was uncommon in colorectal cancer (CRC). The aim of this study was to evaluate its characteristics and prognostic factors through a retrospective analysis.
***Methods.*** Between April 2002 and March 2012, 90 cases including 55 (61.1%) synchronous and 35 (38.9%) metachronousreceiving oophorectomy due to metastasis from CRC in Taipei Veterans General Hospitaland Taichung Veterans General Hospitalwere reviewed. The clinicopathologic data and prognosis were analyzed.
***Results.*** Median age was 51 years. Median duration of survival after OM was 24.3 months. Synchronous group had higher extent of extra-ovary metastasis and lower R0 resection rate than metachronous group, but similar survival curves since diagnosis of OM. None of the T status of primary CRC was less than T3. The sensitivity of CEA (5 ng/ml) and CA-125 (37 u/mL) in OM was 72.2% (65/90), and 65.5% (36/55) respectively. Bilateral ovarian involvement was noted in 65.8%. Peritoneal seeding was the most common site of concurrent metastasis (45.5%), followed by liver (23.3%), lung (17.8%) and retroperitoneal lymphadenopathy (16.7%). CEA before oophorectomy, T4 stage and perineural invasion of primary tumor reached significance in multivariate analysis.
***Conclusions.*** Median duration of survival after OM was 2 years without difference between synchronous and metachronous groups. Bilateral oophorectomy should be suggested to all cases of OM because of the high incidence of bilateral involvement. T4 status and perineural invasion of primary tumor, and pre-oophorectomy CEA were three independent prognostic factors of CRC origin OM.
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Ovarian metastasis (OM) was uncommon in colorectal cancer (CRC), and accounted for less than 10% of all metastasis.[1] Metastatic ovarian tumor represented 30% of whole ovarian tumors.[2] Among OM, incidence of CRC origin had been reported from 7 to 38%.[3-5] Multiple mechanisms have been proposed for tumors spreading to ovary, including hematogenous, trancoelomic, lymphatic and direct invasion. Neither

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of them was proved to be predominant.[2] Low response to chemotherapy of CRC origin OM was reported,[6,7] while surgery still plays an important role in its treatment.[6] The suggested prognostic factors of OM from CRC remain controversial. The aim of this study was to evaluate its characteristics and prognostic factors through a retrospective analysis.

## Materials and Methods

### Patients

From April 2002 to March 2012, all female cases of CRC receivingelective surgery in Taipei Veterans General Hospitaland Taichung Veterans General Hospital were retrospectively reviewed. Cases of OM were recruited from the prospectively established database. All the OM cases had surgical resection for the primary tumor and oophorectomy for OM. Clinicopathological and survival information were analyzed to identify the prognostic factors. Survival analyses focused on ovarian metastasis survival (OMS), defined as the time since the diagnosis of OM to death or the last follow-up status. Death and recurrence were treated as events, while patients who were still alive at the last follow-up were censored. A specialized pathologist performed the diagnosis of ovarian metastasis from colorectal origin on the basis of CK7, CK20 and CDX2 immuno-histochemistry stain.

Metachronous ovarian metastasis was defined by metastasis found 6 months after the primary tumor being diagnosed. Right side colon referred to tumors located at cecum, ascending colon, hepatic flexure and transverse colon. Left side colon referred to tumors located at splenic flexure, descending colon and sigmoid colon. Resection margin evaluation was defined by the residual classification in the AJCC 7th edition. R0 indicated no residual tumor. R1 and R2 indicated microscopic and macroscopic residual tumors.

### Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS version 16.0, SPSS Inc. Chicago, IL). Statistical analysis was performed using the Student's t-test and analysis of variances for comparison of the means. Qualitative parameters were compared with the chi-squared test. Overall survival was computed using the Kaplan-Meier method and the differences in survival between groups were assessed by the log-rank test. Univariate survival analysis was done for defining significant prognostic factors. Factors with $p < 0.2$ in univariate analysis were further analyzed in multivariate survival analysis using the Cox's regression model (backward elimination - likelihood ratio). Values with $p \leq 0.05$ were considered significant.

## Results

There were 2,072 female cases of CRCduring the study period reviewed. Among the 90 cases of ovarian metastasis diagnosed, 55 (61.1%) were synchronous and 35 (38.9%) were metachronous. Median age was 51.0 (range, 27~86) years old. Four of the 13 patients with rectal cancer had preoperative or postoperative radiation therapy. Eighty-eight cases (97.8%) received post-oophorectomy chemotherapy. Analyses of clinicopathological parameters between these two groups are shown in Table 1. Significant distribution difference in the extent of metastasis (numbers of concurrent metastasis to each organ) and residual tumor degree after resection was found. Synchronous group had higher extent of extra-ovary metastasis and lower R0 resection rate. There was no difference in age; location, T stage, N status of primary colorectal cancer; CEA, CA-125 at OM diagnosis; uni- or bilateral involvement ratio; curative resection ratio; size of primary CRC, or OM size; and adjuvant chemotherapy. Intriguingly, none of the T status of primary CRC was less than T3. The sensitivity of CEA (5 ng/ml) and CA-125 (37 u/mL) in diagnosing OM was 72.2% (65/90), and 65.5% (36/55) respectively. Bilateral oophorectomy was performed in 68 patients, with 45 patients (65.8%) had bilateral ovarian involvement. Unilateral oophorectomy was performed for 22 patients. Of them, 4 cases had previous history of unilateral oophorectomy: 1 for primary ovarian cancer, and 3 for

**Table 1.** Clinicopathologic factors analysis of synchronous and metachronous group

| | All n = 90 | Synchronous n = 55 | Metachronous n = 35 | *p* value |
|---|---|---|---|---|
| Median age | 52.9 ± 12.3 | 54.0 ± 11.8 | 51.0 ± 13.2 | 0.26 |
| Location of tumor | | | | 0.34 |
| Right side colon | 30 | 17 | 13 | |
| Left side colon | 47 | 32 | 15 | |
| Rectum | 13 | 6 | 7 | |
| T Stage | | | | 0.58 |
| T3 | 58 | 34 | 24 | |
| T4 | 32 | 21 | 11 | |
| Node status | | | | 0.65 |
| Positive | 75 | 45 | 30 | |
| Negative | 15 | 10 | 5 | |
| Size of primary[a] | 3.8 ± 2.3 | 4.0 ± 2.2 | 3.7 ± 2.5 | 0.52 |
| Size of ovarian tumor[a] | 9.6 ± 5.9 | 9.3 ± 6.3 | 10.1 ± 5.4 | 0.54 |
| CEA at ovarian metastasis[a] | 68.7 ± 142.9 | 88.5 ± 204.7 | 56.1 ± 82.6 | 0.30 |
| CA125 at ovarian metastasis[a] | 208.6 ± 279.7 | 203.0 ± 363.4 | 212.5 ± 208.8 | 0.90 |
| Oophorectomy for OM | | | | 0.43 |
| Bilateral | 68 | 40 | 28 | |
| Unilateral | 22 | 15 | 7 | |
| Ovarian involvement | | | | 0.28 |
| Bilateral | 45 | 25 | 20 | |
| Unilateral | 45 | 30 | 15 | |
| Degree of residual tumor | | | | < 0.01 |
| R0 | 55 | 28 | 27 | |
| R1 | 12 | 6 | 6 | |
| R2 | 23 | 21 | 2 | |
| Extent of metastasis | | | | < 0.01 |
| Ovary only | 37 | 14 | 23 | |
| Ovary + 1 site | 27 | 17 | 10 | |
| Ovary + ≥ 2 sites | 26 | 24 | 2 | |
| Site of concurrent metastasis | | | | |
| Liver | 21 | 18 | 3 | < 0.01 |
| Lung | 15 | 11 | 4 | 0.29 |
| Peritoneum | 41 | 34 | 6 | < 0.01 |
| Retroperitoneal LAP | 14 | 13 | 1 | 0.02 |

[a] Mean; OM: ovarian metastasis; LAP: lymphadenopathy.

benign diseases. For the 12 cases with one side ovary left, four cases had recurrent OM over the other side of ovary in later years.

Concurrent extra-ovarian metastases were present among 53 cases (58.9%), including liver, lung, peritoneal seeding and retroperitoneal lymphadenopathy (LAP). Besides, there were two cases with metastasis to adrenal gland, one case to small bowel, and one case to bone. Peritoneal seeding was the most common site of concurrent metastasis (45.5%), followed by liver (23.3%), lung (17.8%) and retroperitoneal lymphadenopathy (16.7%).

Median follow-up duration of survivors was 18.6 months (9~106.2). Median time to develop OM in metachronous group was 16.8 months. At the last follow-up, 60 mortalities were alldue to colorectal cancer, whereas 30 patients were alive. Of the surviving cases, 19 patients had progressive disease, 1 patient lost contact and 10 patients had stable disease. If calculated since the initial diagnosis of primary CRC, metachronous group obviously had better overall survival than synchronous group ($p = 0.003$) (Fig. 1A),

but there was no survival difference regarding OMS (Fig. 1B). Median time of OMS was 24.3 months. Three- and five-year rate of ovarian metastasis survival were 27% and 16.2%.

In univariate analysis of OMS, metastasis related factors includingcoexistence of liver, lung or peritoneal metastasis, number of concurrent metastasis; and the primary tumor related factors including pT4 stage, lymphovascular invasion, perineural invasion, and presence of residual tumor (R), were all statistically significant. CEA before oophorectomy didn't reach significance initially in univariate analysis ($p$ = 0.18). However, in multivariate analysis, only CEA before oophorectomy, T4 stage and perineural invasion of primary tumor remained significant. (Table 2)

## Discussion

In this study, three prognostic factors of OM were found. It is intriguing to note that these three were from both metastasis and primary tumor related parameters.

The usefulness of measuring serum CEA in the diagnosis, prognosis, and the management in the follow-up after CRC resection has been previously described.[4]

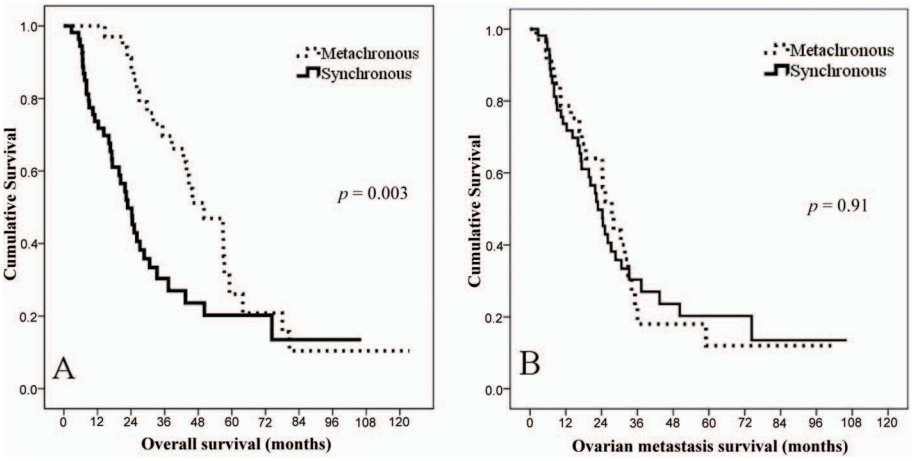


**Fig. 1.** Overall (A) and ovarian metastasis; (B) survival analysis of metachronous and synchronous group.

**Table 2.** Prognostic factors analysis of ovarian metastasis survival

| Variable | Univariate ($p$ value) | Multivariate ($p$ value) | Multivariate Hazard ratio (95% CI) |
|---|---|---|---|
| Age (< 50 vs. > 50) | 0.90 | | |
| Location (rectum vs. colon) | 0.73 | | |
| T stage (T4 vs. T3) | 0.04 | < 0.01 | 3.24 (1.71~6.12) |
| Lymph node (positive vs. negative) | 0.38 | | |
| Degree of residual tumor (R2 or R1 vs. R0) | < 0.01 | 0.45 | |
| Lymphovascular invasion | 0.01 | 0.26 | |
| Perineural invasion | < 0.01 | < 0.01 | 3.20 (1.34~7.62) |
| CEA at oophorectomy (> 6 vs. < 6) | 0.18 | 0.03 | 2.21 (1.07~4.54) |
| CA125 at oophorectomy (> 35 vs. < 35) | 0.77 | | |
| Metachronous vs. synchronous | 0.91 | | |
| Oophorectomy (unilateral vs. bilateral) | 0.99 | | |
| Ovarian involvement (bilateral vs. unilateral) | 0.30 | | |
| Liver metastasis | < 0.01 | 0.06 | |
| Lung metastasis | 0.01 | 0.61 | |
| Peritoneal seeding | 0.02 | 0.38 | |
| Numbers of concurrent metastasis (≥ 2 sites vs. 1 site vs. ovary only) | < 0.01 | 0.49 | |

Elevated CEA is an independent prognostic factor across all stages.[8] In this series, the CEA level at diagnosing OM affects the prognosis of OM, while the initial CEA level of primary tumor diagnosis doesn't. This emphasizes the importance of careful surveillance during follow up. If OM can be found at early stage before CEA highly increases, prognosis would be undoubtedly better. Initially, we expected the existence of extra-ovarian metastasis at diagnosing OM to have an influence on the survival. It evidently revealed so in univariate analysis, but did not appear as such in multivariate analysis. Nearly 60% patients of this study had concurrent extra-ovarian metastasis. Lee et al. reported that cases with concurrent extra-ovarian metastasis showed poorer outcome compared with those of ovarian metastasis only.[9] Segelman et al. reported that peritoneum and liver were the most common sites of metastatic disease.[4,10] Garrett et al. reported that peritoneal seeding was associated with inferior survival.[11] However, Shan et al. stated that there was no survival difference among different metastasis.[12] In our study, peritoneum and liver accounted for the majority of extra-ovarian metastasis. However, only liver metastasis showed a trend related to poor prognosis in multivariate analysis ($p = 0.063$). In a subgroup analysis, we analyzed the data of 44 patients with single site of extra-ovarian metastasis. No difference in survival was found among the liver, lung, peritoneum and retroperitoneal lymphadenopathy groups. The small case number might have an impact on such result. The only factor regarding status of metastasis remained for prognosis, was CEA level.

CA-125 was known initially as a marker for primary ovarian cancer, but was also reported to be elevated in secondary malignant tumors of ovary, including those from CRC.[4] Tan et al. reported elevated CEA level in 86% and CA-125 level in 71% of CRC cases with OM.[13] In this series, CEA and CA-125 levels were abnormal in 74%, and 67% respectively. Both studies revealed a little lower sensitivity rate of CA-125 than CEA for OM. Although, as in the result of Tan et al. that increased sensitivity rate was obtained through the combined usage of CEA and CA-125, we've also reached up to 83.3% here, surveillance with these two markers that lack justification of their specificity and cost-effectiveness remained as a major concern. However, due to the low incidence of OM, we anticipated much difficulty in the attempt to prove it.

Invasion beyond the bowel wall (T4), defined by invasion through serosa, is an independent prognostic factor of OM. In our study, all patients had tumor invasion beyond the muscularispropria (T3 and T4), which was similar to the previous studies.[4,14] This may be applied as a reference rule in the differential diagnosis of OM of CRC. Also, the perineural invasion of primary tumor is another independent factor. Perieneural invasion is the process of neoplastic invasion of nerve, and tumor cells spreading along neural sheaths are privileged to a low-resistance plane, which serves as a conduit for their migration.[15] It is a well-accepted route of metastatic spread even in the absence of lymphatic or vascular invasion. Incidence of perineural invasion was from 22 to 33% in previous studies.[16] In CRC, it indicates a more aggressive tumor phenotype. In this study, perineural invasion was found in 20.8%, a figure similar to the previous studies.[15] We suggest that when OM is noted, detailed examination of primary tumor pathology should be conducted to search for these two factors.

It has been reported that the increasing incidence of CRC origin OM, especially in Asian countries, had made it the 2$^{nd}$ most common cause of OM.[2,17] Other study indicated better survival from CRC origin than gastric or breast cancer origin.[18] These evidences disclose the importance and worthiness of careful surveillance of OM. Our study was the first study that thoroughly analyzed the prognostic factors associated with post-oophorectomy survival. As note in Table 3, our series showed comparable survival results with other series.[4,10,11,13,19-28] The difference among these studies might be owing to the heterogeneouscase population, including (1) ratio of patients selectied from metachronous group and synchronous group, (2) ratio of patients with isolated ovarian metastasis to concurrent extraovarian metastasis, and (3) ratio of patients receiving oophorectomy and adjuvant chemotherapy or chemotherapy only.

OM is usually obscure, thus easily leading to misdiagnosis. It has been reported that 45% of OM from primary CRC was misdiagnosed as primary ovarian

**Table 3.** Reported series of ovarian metastasis from colorectal cancer

| Series | Year | N | Median age (year) | Metachronous/ synchronous | Median overall survival (mo) | 5-year survival (%) |
|---|---|---|---|---|---|---|
| Huang et al.[19] | 1998 | 155 | 55[a] | 65/90 | | 24/15[b] |
| Rayson et al.[20] | 2000 | 38 | 54.5 | 11/27 | 31 | |
| Wright et al.[21] | 2004 | 28 | 55 | 28/0 | 18.4 | |
| Sakakura et al.[22] | 2004 | 9 | 60.3 | 0/9 | 20.8 | |
| Ayhan et al.[23] | 2005 | 33 | 49.1 | | 48 | |
| Erroi et al.[24] | 2006 | 10 | 46 | 7/3 | 36 | |
| McCormick et al.[25] | 2007 | 39 | | | 30 | |
| Omranipour et al.[26] | 2009 | 13 | 40 | 8/5 | 20/10[a,b] | |
| Kim et al.[27] | 2009 | 103 | 46[a] | 29/74 | | 26.6 |
| Tan et al.[13] | 2009 | 25 | 53 | 9/16 | 19 | 20.2 |
| Fujiwara et al.[4] | 2010 | 22 | 54.1[a] | 14/8 | 34.9 | 43.8 |
| Segelman et al.[10] | 2010 | 65 | - | 23/42 | | 22/11[b] |
| Ojo et al.[28] | 2011 | 26 | 52.5/45.5[b] | 4/22 | 27.5 | 9 |
| Garrett et al.[11] | 2012 | 110 | 50/49[b] | 39/71 | 50/39.4[b] | |
| Current study | 2013 | 90 | 51 | 35/55 | 50.1/22.8[b] | 21.8 |

[a] Mean; [b] metachronous/synchronous.

cancer.[23] For metachronous OM, reported median time of OM diagnosed after primary tumor resection ranged from 12 to 22.4 months.[4,10,11,14,22] Kim et al. reported 82% relapse within 3 years.[27] Median time of relapse in this series was 16.8 months. During this vulnerable time of OM, close follow up with multiple modalities including CT scan, sonogram and tumor marker is recommended. We consider selective use of CA-125 in differentiation as a helpful tool among suspected cases.

In this study, we've found similar result as before that OM usually comes with bilateral involvement. Bilateral oophorectomy should therefore be suggested for all cases of CRC OM.

There are several limitations to our study. As a retrospective design, it was based on charts review. The incidence might be underestimated because those OM caseswho didn't have significant symptomswere neither treated nor enrolled in the study. Also, we didn't have enough data to analyze the effects of chemotherapy and surgery.

## Conclusion

Median time of OMS was around 2 years with no difference between synchronous and metachronous groups. Bilateral oophorectomy should be suggested to all cases of OM because of the high incidence of bilateral involvement. T4 status and perineural invasion of primary tumor, and pre-oophorectomy CEA were the three independent prognostic factors of CRC origin OM.

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**原　著**

# 大腸癌合併卵巢轉移之臨床表現及預後因子

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**目的**　大腸癌合併卵巢轉移在臨床上屬於少見案例。針對此群少數病患進行臨床特徵及相關因子做預後分析。

**方法**　自 2002 至 2012 年間，台北榮民總醫院與台中榮民總醫院共有 90 位病患接受大腸癌及卵巢切除手術，其中有 55 位 (61.1%) 為同時性，有 35 位 (38.9%) 為異時性，此篇文章針對這 90 病患進行回顧性研究分析。

**結果**　在這 90 位病患中，平均年齡為 51 歲。從發現卵巢轉移到死亡的時間中位數為 24.3 個月。同時性卵巢轉移的病患比異時性的病患有較高的比例合併卵巢以外的轉移及較低的腫瘤完全切除率，但兩者的存活率則差不多。這些腫瘤的 T stage 都在 T3 以上。CEA 及 CA-125 對於卵巢轉移的敏感度分別為 72.2% (65/90) 及 65.5% (36/55)。兩側卵巢侵犯的比例為 65.8%。最常見的卵巢外轉移依序是腹膜轉移 (45.5%)、肝臟 (23.3%)、肺臟 (17.8%) 及後腹腔淋巴結 (16.7%)。卵巢切除前 CEA 升高、T4 及腫瘤細胞沿著神經生長散布為多變項存活分析的預後因子。

**結論**　不論在異時性或是同時性轉移的病人，大腸癌合併卵巢轉移之後的存活時間約為兩年。卵巢轉移的病人因兩側轉移的機會較高，建議行兩側卵巢切除。卵巢切除前 CEA 升高、T4 及腫瘤細胞沿著神經生長散布為多變項存活分析的預後因子。

**關鍵詞**　大腸癌、卵巢轉移、異時性、同時性。