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ORIGINAL ARTICLE

# Survival benefit from ovarian metastatectomy in colorectal cancer patients with ovarian metastasis: a retrospective analysis

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**Abstract**
*Purpose* A recent study demonstrated that colorectal cancer (CRC) with ovarian metastases was less responsive to chemotherapy compared with extraovarian metastases. Hence, the ovary may actually represent a "sanctuary" for metastatic cells from CRC. The aim of the study was to investigate the impact of ovarian metastatectomy on survival of CRC patients with ovarian metastasis.
*Methods* Between 1996 and 2008, 83 CRC patients underwent an oophorectomy. For the historical control, 47 CRC patients with ovarian metastasis without resection were included in the analysis.
*Results* The median age was younger (48 years) in the oophorectomy group compared with the historical control (54 years; $P = 0.012$). The proportion of synchronous metastasis was higher in the oophorectomy group than in the control group (57 vs. 30%; $P = 0.003$). After a median follow-up duration of 60.8 months (range of 7.4–169.7 months), the median OS was significantly longer in the oophorectomy group (28.1 vs. 21.2 months, oophorectomy vs. non-oophorectomy; $P = 0.038$). For ovary-specific survival (date of ovarian metastasis diagnosis to death), CRC patients with an oophorectomy showed a significantly more favorable survival rate than the control group (20.8 vs. 10.9 months; $P < 0.001$). In univariate analyses, oophorectomy ($P = 0.038$), unilaterality of ovarian metastasis ($P = 0.032$), metastasis confined to ovaries ($P < 0.001$), normal CEA level ($P < 0.001$), good performance status ($P = 0.001$), palliative chemotherapy ($P = 0.001$), and primary disease resection ($P = 0.005$) were identified as significantly good prognostic factors for overall survival. The oophorectomy, chemotherapy, metastasis confined to ovaries, normal CEA level, and good performance status retained statistical significance at the multivariate level ($P = 0.003$, $P = 0.004$, $P = 0.005$, $P = 0.015$, and $P = 0.029$, respectively).
*Conclusions* Based on this retrospective analysis, the ovarian metastatectomy significantly prolonged survival in CRC patients with ovarian metastases. The potential role of an ovarian metastatectomy in the management of CRC should be prospectively studied.

**Keywords** Colorectal cancer · Ovarian metastasis · Ovarian metastatectomy · Survival benefit

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## Introduction

In Western countries, colorectal cancer (CRC) is the most common non-gynecologic malignancy resulting in metastases to the ovaries [11], with an incidence of 2–8% in women undergoing surgical resection of a primary CRC [2]. In the past decade, remarkable progress has been achieved in the treatment of metastatic CRC, especially following the introduction of an effective combination of chemotherapy regimens containing oxaliplatin, irinotecan, and

**Table 1** Patient characteristics

| | Oophorectomy group $n = 83$ (%) | Non-oophorectomy group $n = 47$ (%) | Total $n = 130$ (%) | $P$ value |
|---|---|---|---|---|
| Age (median) | 48 | 54 | 51 | 0.012 |
| Years of enrollment | | | | |
| 1996–2002 | 29 (35) | 11 (23) | 40 (31) | 0.171 |
| 2003–2008 | 54 (65) | 36 (77) | 90 (69) | |
| Menstrual status | | | | |
| Premenopause | 50 (56) | 21 (39) | 71 (55) | 0.085 |
| Postmenopause | 33 (44) | 26 (61) | 59 (45) | |
| Location of primary tumor | | | | |
| Colon | 72 (87) | 40 (85) | 112 (86) | 0.795 |
| Rectum | 11 (13) | 7 (15) | 18 (14) | |
| Histology | | | | |
| WD, MD | 66 (97) | 32 (86) | 98 (93) | 0.094 |
| PD, signet ring cell | 2 (3) | 5 (14) | 7 (7) | |
| Primary tumor resection | 78 (94) | 37 (79) | 115 (89) | 0.009 |
| Timing of metastasis | | | | |
| Synchronous | 47 (57) | 14 (30) | 61 (47) | 0.003 |
| Metachronous | 36 (43) | 33 (70) | 69 (53) | |
| CEA | | | | |
| Normal | 21 (27) | 7 (16) | 28 (23) | 0.165 |
| Elevated | 57 (73) | 37 (84) | 94 (77) | |
| Extent of metastasis | | | | |
| Ovarian metastasis only | 30 (36) | 0 (0) | 30 (23) | <0.001 |
| Extraovarian metastasis | 53 (64) | 47 (100) | 100 (77) | |
| ECOG Performance status | | | | |
| 0–1 | 76 (92) | 43 (91) | 119 (92) | 1.000 |
| ≥2 | 7 (8) | 4 (9) | 11 (8) | |
| Symptoms | 48 (58) | 9 (19) | 57 (44) | <0.001 |
| Ovary involvement | | | | |
| Unilateral | 38 (46) | 24 (51) | 62 (48) | 0.562 |
| Bilateral | 45 (54) | 23 (49) | 68 (52) | |
| Chemotherapy | 66 (83) | 38 (81) | 104 (82) | 0.816 |

bevacizumab [8]. These novel agents have yielded both higher tumor response rates and prolonged overall survival.

Despite this substantial improvement in survival, ovarian metastases still have a poorer prognosis than other metastatic sites in patients with CRC [6, 16]. It is currently unclear whether this adverse prognosis reflects merely a more advanced disease stage, intrinsic disease aggressiveness, or less sensitivity to systemic chemotherapy of ovarian metastases compared with extraovarian metastases [13]. These uncertainties complicate the optimal management of ovarian metastases from CRC, especially in the case of simultaneous extraovarian metastases, which are present in 50–70% of the cases.

A recent study demonstrated that CRC with ovarian metastases was less responsive to chemotherapy compared with extraovarian metastases [3]. Another study reported that the tumor response rate to 5-FU-based chemotherapy was 40% for extraovarian sites but only 5% for ovarian metastases [13]. In support of this observation, there was no objective tumor response of ovarian metastases, whereas the tumor control rate for extraovarian metastatic lesions was 65% in a series of 22 CRC patients with ovarian metastases [3]. Based on these reports, the ovary has been suggested as a third "sanctuary" organ for systemic chemotherapy for solid tumors. Although the underlying mechanism for the relative resistance to chemotherapy needs to be determined, several features such as voluminous, cystic, and mucin-rich nature may contribute to poor sensitivity to chemotherapy.

Hence, we undertook this study to analyze the clinical impact of ovarian metastases on the survival of CRC patients and to evaluate treatment outcomes after an oophorectomy followed by chemotherapy.

## Patients and methods

We retrospectively reviewed the medical records of the patients with histopathologically proven CRC and ovarian metastasis between January 1996 and December 2008. For the oophorectomy group, we searched for CRC patients who had gynecologic surgery, reviewed their records, and found a total of 83 patients. For the non-oophorectomy group, we searched for CRC patients who had solid masses of their ovary in follow-up computed tomography images and found a total of 47 patients. In this series, synchronous ovarian metastases were defined as those that were diagnosed less than 180 days from the time at which the primary CRC was diagnosed. In total, 130 patients were included in this study. Each patient's medical records included information on age, sex, histologic type, TNM stage, extent of metastasis, menstruation status, Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, treatment details, and vital status. The study was performed after being approved by the Institutional Review Boards at the Samsung Medical Center in Seoul, Korea.

### Treatment

A bilateral or unilateral oophorectomy was performed by transabdominal laparotomy through a low midline incision. A hysterectomy was added to remove the tumor from the ovary(ies) more completely at the discretion of the surgeon. Surgical findings on residual tumors of the abdomen and pelvis were systematically documented. All standard chemotherapeutic regimens, including FOLFOX, FOLFIRI, XELIRI, XELOX ± avastin, or cetuximab, were given at the physician's discretion or the patient's preference.

### Statistical methods

Overall survival was defined as the time from the pathologically confirmed date of a tumor to the date of death or the last follow-up. Progression free survival was defined as the time from the date of the start of treatment to the date of documented disease progression or death from any cause. Kaplan–Meier estimates were used in the analysis of the time-to-event variables and the 95% confidence interval (CI) for the median time to event was computed. Comparisons of survival by univariate analysis were estimated by the log-rank test. Cox's proportional hazard model was used for multivariate analyses. A $P$ value of less than 0.05 ($P < 0.05$) was considered to be statistically significant. For the oophorectomy group, ovary-specific survival was defined as the time from tissue diagnosis of ovarian metastases to death or the last follow-up status. For the control group, ovary-specific

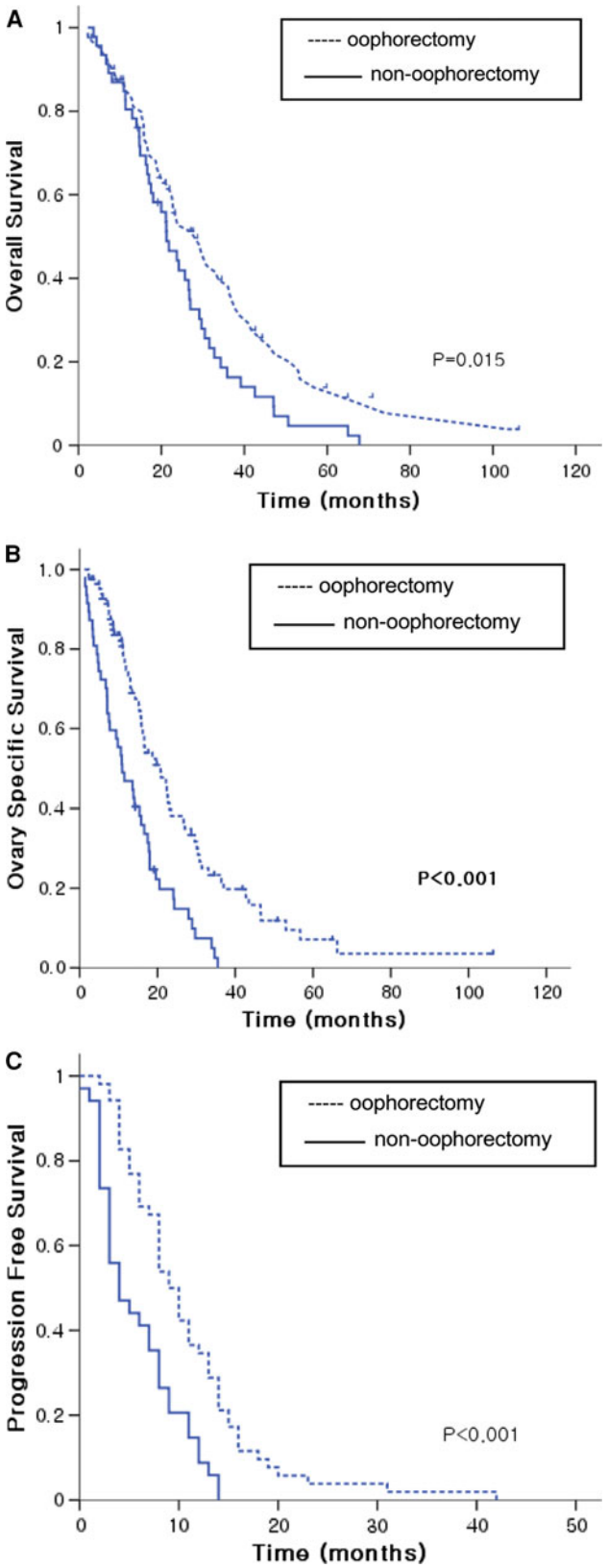


**Fig. 1** Survival according to oophorectomy. **a** Overall survival, **b** Ovary-specific survival, **c** Progression free survival

survival was defined as the time from the image diagnosis of ovarian metastasis to death or the last follow-up status.

## Results

Of the 130 patients included in this analysis, 83 (63.8%) patients received an oophorectomy and 47 (36.2%) patients did not. No one who underwent an oophorectomy had related complications. The clinical characteristics of the patients in the two groups are summarized in Table 1. The median age at the time of the diagnosis of ovarian metastasis was 48 years in the oophorectomy group and 54 years in the chemotherapy alone group ($P = 0.012$). The time period of enrollment was not significantly different between the two groups. The proportions of primary tumor resection and synchronous ovarian metastasis were slightly higher in the oophorectomy group compared with the chemotherapy alone group. Notably, all 47 patients who received upfront chemotherapy had extraovarian metastases, while only two-thirds of the patients (53/83) in the oophorectomy group had extraovarian metastasis ($P < 0.001$). There was not a significant difference in the percentage of patients who received palliative chemotherapy between the two groups ($P = 0.816$). Patients underwent an oophorectomy for the following reasons: synchronous metastatectomy with primary tumor resection ($n = 37$), initial presentation with ovarian metastases ($n = 24$), alleviation of symptom d/t ovarian mass ($n = 16$), and others ($n = 6$). An oophorectomy was performed with a primary tumor resection in 39 patients, and an oophorectomy was done separately with a primary tumor resection in 44 patients. Of these 44 patients, 5 patients did not have a primary tumor resection, 36 had metachronous ovarian metastasis, and 3 had synchronous metastasis but underwent an oophorectomy more than 6 months after their primary tumor resection.

### Response and survival

After a median follow-up duration of 60.8 months (range of 7.4–169.7 months), the median survival was significantly longer for the oophorectomy group compared with the control group (28.1 vs. 21.2 months; $P = 0.015$; Fig. 1a). Moreover, the median ovary-specific survival after a diagnosis of ovarian metastasis was 20.8 months for the oophorectomy group and 10.9 months for the control group ($P < 0.001$; Fig. 1b). In terms of progression-free survival, there was a substantial prolongation in the oophorectomy group compared with the control group (15.6 vs. 6.1 months; $P < 0.001$; Fig. 1c). We conducted subgroup analysis that included only the patients who had extraovarian metastasis ($n = 100$; Fig. 2). Median ovary-specific survival was 15.7

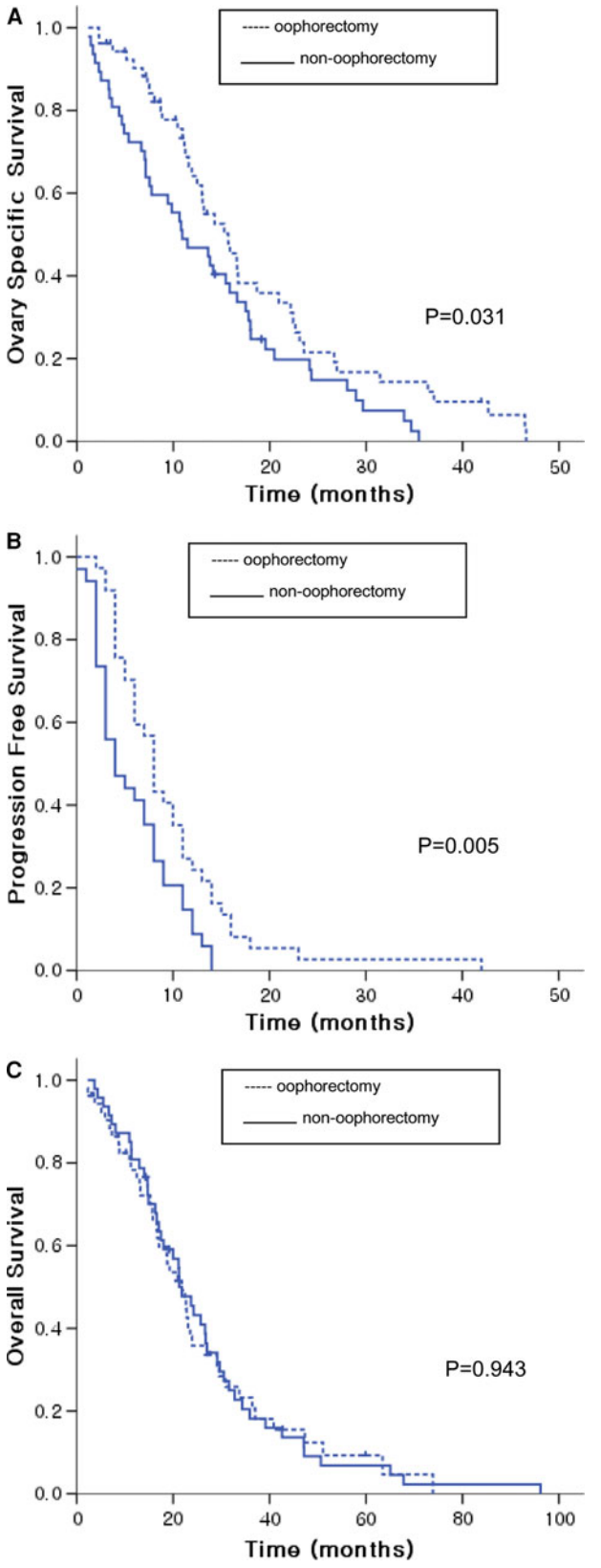


**Fig. 2** Subgroup survival analysis in patients with extraovarian metastasis. **a** Ovary-specific survival, **b** Progression-free survival, **c** Overall survival

and 10.9 months ($P = 0.031$), and progression-free survival was 8.0 months and 4.0 months ($P = 0.005$) for the oophorectomy group and non-oophorectomy group, respectively, while the overall survival was not significantly different (21.8 vs. 21.2 months; $P = 0.943$).

Of the 38 patients who received only chemotherapy, 33 could be evaluated for a treatment response. Of these 33, 15 received oxaliplatin-based chemotherapy, 14 received irinotecan-based chemotherapy, and 4 had capecitabine alone. Their responses to chemotherapy were evaluated according to ovarian versus extraovarian metastatic sites for 33 patients. Responses to chemotherapy were considerably lower in ovarian metastases compared with the chemoresponsiveness of extraovarian metastases (6/33 or 18.2% vs. 11/33 or 33.3%; $P < 0.001$; Fig. 3).

### Prognostic factor analysis

The clinical factors predicting survival after ovarian metastasis was detected during univariate analysis by a log-rank test are shown in Table 2. Primary tumor resection ($P = 0.005$), oophorectomy ($P < 0.001$), normal range CEA ($P < 0.001$), absence of extraovarian metastases ($P < 0.001$), good performance status ($P < 0.001$), and palliative chemotherapy ($P = 0.001$) significantly predicted favorable survival. We performed multivariate analysis and included the factors that were statistically significant in univariate analysis for survival. Prognostic factors for survival that retained statistical significance at the multivariate level were no oophorectomy ($P = 0.005$; RR, 1.954; 95% CI, 1.220, 3.130), presence of extraovarian metastases ($P = 0.003$; RR, 2.823; 95% CI, 1.438, 5.543), elevated CEA ($P = 0.007$; RR, 2.216; 95% CI, 1.240, 3.960), and poor performance ($P = 0.032$; RR, 2.338; 95% CI, 1.077, 5.077) (Table 3). Thus, in this analysis, CRC patients with ovarian metastases who are associated with extraovarian metastases, elevated CEA, and poor performance, but no oophorectomy, showed a two- to threefold increased risk of death.

## Discussion

Although this study is a retrospective analysis, this study represents the largest one focused on 130 CRC patients with ovarian metastases. Based on our analysis, patients with ovarian metastases who underwent an oophorectomy before chemotherapy survived significantly longer than those without an oophorectomy (28.1 vs. 21.2 months, respectively; $P = 0.015$). Importantly, no oophorectomy was an independent prognostic factor for poorer survival with a relative risk of 1.954 in the multivariate analysis. Thus, the removal of ovarian metastases seemed to confer a survival benefit in CRC patients with ovarian metastases.

Modern chemotherapy using cytotoxic agents alone offers an extension of median survival time of approximately 2 years to patients with metastatic CRC [4, 5, 14]. When monoclonal biologic agents are added to cytotoxic chemotherapy, the median survival time extends beyond 2 years, with 20% of the patients alive at 4 years after their diagnosis of metastatic disease [1, 7]. Importantly, with the advent of newer cytotoxic agents along with biologics, the conversion rate from unresectable metastatic disease to resectable disease has appreciably increased in the past decade [9, 12]. Given the survival benefit from a liver metastatectomy, more aggressive surgical intervention should be considered for CRC patients, especially those with chemo-resistant ovarian metastases.

In accordance with previous studies, the ovarian response was lower than the extraovarian response in 33 evaluable patients in our series (18.2 vs. 33.3%; $P < 0.001$). In D. Goere's study, the ovarian response was 0% to cytotoxic chemotherapy, while the extraovarian response was 35% in 20 evaluable patients [3]. Whether the ovary is a true sanctuary site for chemotherapy needs to be validated in more prospective trials. Of note, not only was the response rate was low, but 60% of the ovarian metastases did not change in size during the course of cytotoxic chemotherapy.

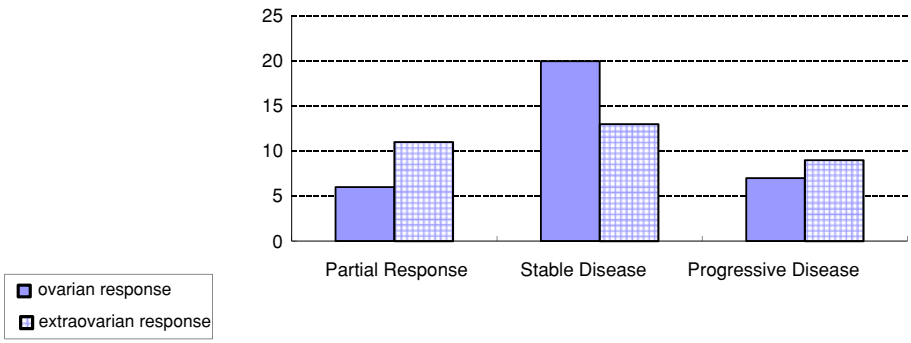


**Fig. 3** Response to chemotherapy in the non-oophorectomy group ($n = 33$)

| | PR | SD | PD |
|---|---|---|---|
| Ovarian response | 6 | 20 | 7 |
| Extraovarian response | 11 | 13 | 9 |

**Table 2** Univariate analysis for survival

| | No. of patients (%) | Median survival (months) | *P* value |
|---|---|---|---|
| Age | | | |
| ≤65 years | 88 (68) | 17.8 | 0.399 |
| >65 years | 42 (32) | 14.1 | |
| Menstrual status | | | |
| Premenopause | 71 (55) | 16.2 | 0.586 |
| Postmenopause | 59 (45) | 16.6 | |
| Primary site | | | |
| Colon | 112 (86) | 15.9 | 0.787 |
| Rectum | 18 (14) | 20.8 | |
| Histologic type | | | |
| WD, MD | 98 (93) | 16.6 | 0.603 |
| PD, signet ring cell | 7 (7) | 18.0 | |
| Primary tumor resection | | | |
| (+) | 115 (89) | 16.7 | 0.005 |
| (−) | 15 (11) | 7.1 | |
| Ovarian resection | | | |
| (+) | 83 (64) | 20.8 | <0.001 |
| (−) | 47 (36) | 10.9 | |
| Timing of metastasis | | | |
| Synchronous | 61 (47) | 16.7 | 0.650 |
| Metachronous | 69 (53) | 15.9 | |
| CEA | | | |
| Normal | 28 (23) | 33.9 | <0.001 |
| Elevated | 94 (77) | 15.7 | |
| Extent of metastasis | | | |
| Ovarian metastasis only | 30 (23) | 30.4 | <0.001 |
| Extraovarian metastases | 100 (77) | 13.8 | |
| ECOG Performance status | | | |
| 0–1 | 119 (92) | 16.7 | 0.001 |
| ≥2 | 11 (8) | 6.8 | |
| Laterality | | | |
| Unilateral | 62 (48) | 20.8 | 0.032 |
| Bilateral | 68 (52) | 14.3 | |
| Chemotherapy | | | |
| (+) | 104 (82) | 17.8 | 0.001 |
| (−) | 23 (18) | 10.4 | |

**Table 3** Multivariate analysis for survival (ovary-specific survival)

| | *P* value | Relative risk (Exp. B) | 95% CI for Exp. B | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Oophorectomy (−) | 0.005 | 1.954 | 1.220 | 3.130 |
| Extraovarian metastasis (+) | 0.003 | 2.823 | 1.438 | 5.543 |
| Elevated CEA | 0.007 | 2.216 | 1.240 | 3.960 |
| Poor performance | 0.032 | 2.338 | 1.077 | 5.077 |
| No chemotherapy | 0.004 | 2.332 | 1.305 | 4.168 |
| No 1' tumor resection | 0.305 | 1.440 | 0.717 | 2.892 |
| Bilateral involvement | 0.078 | 1.484 | 0.957 | 2.300 |

Clearly, this study is limited by its retrospective analysis in nature. In particular, the proportion of synchronous ovarian metastases and the metastasis confined to ovaries was higher in the oophorectomy group (Table 1). In order to minimize bias from discrepancies in the percentages of synchronous or metachronous ovarian metastases, we analyzed ovary-specific survival, which was defined as the date of diagnosis of ovarian metastasis to the last follow-up date. The median ovary-specific survival after the diagnosis of ovarian metastasis was 20.8 months for the oophorectomy group and 10.9 months for the control group ($P < 0.001$). Thus, both overall survival and ovary-specific survival were substantially prolonged by an oophorectomy in our series. We also conducted subgroup analysis that included the patients who had extraovarian metastasis to minimize the selection bias of our study ($n = 100$; Fig. 2). In accordance with the results of all patients with ovarian metastasis, ovary-specific survival and progression-free survival were significantly longer in the oophorectomy group. However, overall survival was not significantly different. One of the plausible explanations would be a higher proportion of metachronous patients in the non-oophorectomy group when compared with the oophorectomy group in this study.

Although the inherent bias from retrospective analysis cannot be eliminated, this study showed that an oophorectomy was an independent predictor of better survival in multivariate analyses, which strongly suggests a potential survival benefit from an oophorectomy after ovarian metastases are diagnosed.

At the present time, there is only one randomized prospective trial of a prophylactic oophorectomy for CRC [15]. During the period of 11 years, 155 patients were randomized for an oophorectomy or no oophorectomy at laparotomy for resection of CRC. This trial suggested a survival benefit of an oophorectomy at between 2 and 3 years after surgery, but Kaplan–Meier survival analysis indicated that this was not statistically significant and the benefit did not appear to persist for 5 years. In terms of recurrence-free survival, there was a more substantial separation of the curves, with 80 versus 65% 5-year, disease-free survival for oophorectomy versus non-oophorectomy with no statistical significance [15].

There is also a retrospective study on a prophylactic oophorectomy for advanced rectosigmoid cancer [10]. In this study, the patients who presented with ovarian cystic lesions, the tethering of the ovary to the primary rectosigmoid tumor or pelvic ascites accumulation, which were postulated as the indicative findings for the synchronous ovarian micrometastasis, underwent an oophorectomy in

addition to standard anterior or lower anterior resections. Patients undergoing a prophylactic oophorectomy plus an N3 lymphadenopathy achieved a good treatment outcome, with an estimated 5-year survival rate of 62.5 and 69.2% in patients with and without ovarian micrometastasis, respectively ($P = 0.917$). A prospective study on the usefulness of an oophorectomy is definitely warranted for metastatic CRC patients.

Given that an oophorectomy is associated with a low rate of perioperative morbidity, an oophorectomy may be a feasible option for CRC patients with ovarian metastases. In addition, a metastatectomy should be aggressively evaluated for CRC patients with ovarian metastases.

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