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Original Research Article

The Validity of a New Edition of Classification for Ovarian Metastasis from Colorectal Cancer

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Abstract

Objectives: In the 9th edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (JCCRC), ovarian metastasis is classified as distant metastasis. We assessed the significance of resection of ovarian metastases and the validity of this 9th edition of JCCRC for ovarian metastases from colorectal cancer (CRC).

Methods: We retrospectively analyzed the clinicopathological factors and overall survival of 17 patients with ovarian metastases from CRC who underwent resection and 110 female CRC patients with Stage IV (M1a) disease.

Results: The patients with only ovarian metastases who underwent resection had a longer median survival time than patients with both ovarian and peritoneal metastases who underwent resection (45.4 months vs. 9.3 months, $P = 0.029$). The 5-year overall survival of the patients with only ovarian metastases who underwent R0 resection was as long as that of the female Stage IV (M1a) CRC patients after R0 resection (50% vs. 48%, $P = 0.334$).

Conclusions: We found that, after resection, patients with only ovarian metastases had significantly better prognoses than patients with ovarian and peritoneal metastases. R0 resection of ovarian metastasis indicated as good prognosis as R0 resection of metastasis to one distant organ without ovaries. So the 9th edition of JCCRC, which classifies ovarian metastasis from CRC as distant metastasis, is appropriate.

Keywords

colorectal cancer, ovarian metastasis, peritoneal metastasis

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Introduction

In 8th edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (JCCRC), patients with metastasis localized to adjacent peritoneum from colorectal cancer (CRC) were classified as P1, and patients with limited metastasis to distant peritoneum were classified as P2. When CRC patients have ovarian metastasis, but not peritoneum metastasis, they were classified as P2. If CRC patients have diffuse metastasis to distant peritoneum, they were classified as P3. In July 2018, JCCRC[1] was revised. The 9 th edition of the classification defines M1a as distant metastasis from CRC to one organ without peritoneal metastasis, such as the liver, lung, or ovary, M1b as distant metastasis in more than one organ without peritoneal metastasis, and M 1c as peritoneal metastases. Additionally, M1c is divided into two M1c1 as metastasis to the peritoneum only, and M1 c2 is metastasis to the peritoneum with other distant metastases. This revision changed the classification of ovarian metastases from peritoneal metastasis to distant metastasis.

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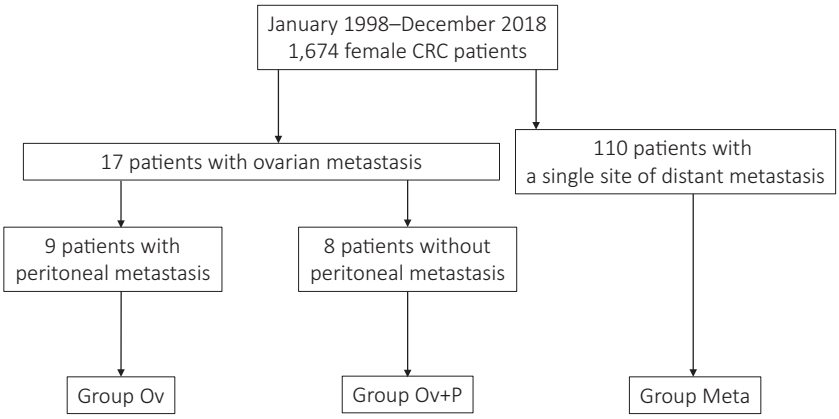

Figure 1. Flow chart of the analyzed patients.
We divided female CRC patients with ovary metastasis and other distant metastasis into three groups.

Fujiwara et al.[2] and Erroi et al.[3] reported that aggressive resection of ovarian metastases from CRC is associated with better overall survival. Few studies have assessed the prognoses of CRC patients with ovarian metastases.

We retrospectively investigated clinicopathological characteristics and prognoses after R0 resection of patients with only ovarian metastasis from CRC and female CRC patients with a single distant metastasis, which are classified in the same stage under the 9th edition of classifying system.

Methods

Patients

Between January 1998 and December 2018, 3,909 CRC patients underwent resection at the Toyonaka Municipal Hospital. Among these, there were 1,674 female patients (42.8%), including 17 (1.0% of the female CRC patients) who underwent resection of ovarian metastases from primary CRC. We divided these 17 patients into two groups: nine who had no peritoneal metastasis (Group Ov), and eight who had peritoneal metastasis (Group Ov+P). At the same time, 110 female CRC patients with metastasis to a single distant site (excluding the ovary) also underwent surgical resection (Group Meta) (Figure 1).

Patient follow-up system

After surgery, all patients received the following for follow-up: a physical examination, serum tumor marker, and chest computed tomography (CT). Abdominal and pelvic CT was performed every three to six months for the first three years and every six months for the next two years, and colonoscopy was performed every one to two years. When a swollen ovary was detected and diagnosed as distant metastasis, surgical resection was considered.

Statistical analyses

A t-test and chi-square test compared patients' characteristics and clinicopathological factors. The statistical analysis was performed using the JMP pro 14 software program (SAS Institute Inc. United States). The survival curves were estimated using the Kaplan-Meier technique and were compared by the log-rank test. P values of <0.05 were considered statistically significant.

Ethical approval

The research ethics committee of Toyonaka Municipal Hospital approved this study (IRB No 2019-03-09). We obtained informed consent in the form of opt-out on the website and excluded those who opted out. This study's conduct followed the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Table 1 summarizes the clinicopathological characteristics of Group Ov and Group Ov+P. The median age of the 17 patients was 66 years old. Seven primary tumors were in the right colon, five were in the left colon, and five were in the rectum. More than half of all tumors were tubular adenocarcinoma (n = 11), and the others were mucinous adenocarcinoma (n = 3) and papillary adenocarcinoma (n = 1); two were unknown. Regarding the RAS status, 11 patients were wild type, three were mutant type, and three were unknown.

There were no significant differences in the serum tumor marker levels between Group Ov and Group Ov+P. In Group Ov+P, emergency operations were performed more frequently because of intestinal obstruction ($P = 0.043$).

We defined synchronous and metachronous metastasis according to the criteria used by Warren and Gates[4]. Synchronous metastasis referred to tumors detected less than

Table 1. Characteristics of Patients in Group Ov and Group Ov+P.

	Group Ov (n = 9)	Group Ov+P (n = 8)	*P* value
Age (median, years)	52 (42-79)	71 (44-76)	0.404
Location of primary tumor (Right Colon/Left Colon/Rectum)	3/3/3	4/2/2	
Histology (pap/tub/muc/unknown)	0/7/1/1	1/4/2/1	
RAS status (wild/mutant/unknown)	6/2/1	5/1/2	
CEA (median, ng/mL)	33 (1.2-629.4)	22 (1.6-1161.8)	0.836
CA19-9 (median, U/mL)	49 (2-458)	33 (2-661)	0.721
Surgical plan (Scheduled/Emergency)	9/0	5/3	0.043
Timing of resection (Synchronous/Metachronous)	7/2	2/6	0.030
Operative procedure (BSO/USO)	8/1	5/3	0.200
Side of disease (Unilateral/Bilateral)	5/4	5/3	0.772
Residual tumor classification (R0/R1, 2)	9/0	0/8	<0.005
Adjuvant chemotherapy (Yes/No)	8/1	6/2	0.453
Follow-up period (median, months)	33 (3-80)	12 (8-21)	

pap: papillary adenocarcinoma, tub: tubular adenocarcinoma, muc: mucinous adenocarcinoma,
CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9,
BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy

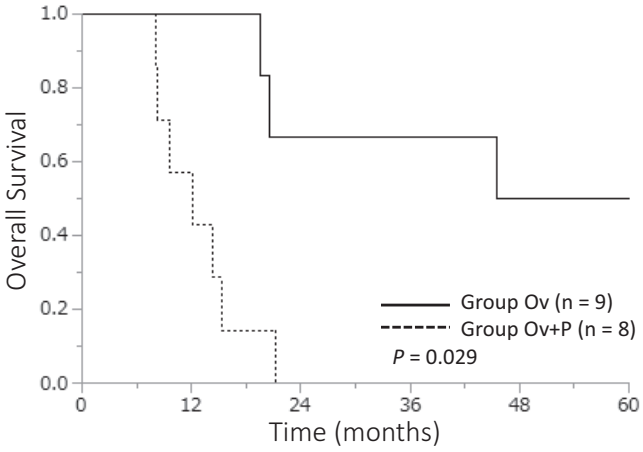

Figure 2. Kaplan-Meier curves of the overall survival of patients with ovarian metastases (Group Ov vs. Group Ov+P). Group Ov had a significantly better prognosis than Group Ov+P.

one year after the resection of the primary tumor, and metachronous metastasis referred to tumors detected after one year or longer. Nine patients were diagnosed with ovarian metastasis synchronously, and eight patients were diagnosed with metachronous metastases. Thirteen patients underwent bilateral salpingo-oophorectomy (BSO), and four underwent unilateral salpingo-oophorectomy (USO). All patients in Group Ov underwent R0 resection, whereas all patients in Group Ov+P underwent R1 or R2 resection.

Overall survival (OS) curves are shown for patients with ovarian metastases (n = 17), using the Kaplan-Meier technique (Figure 2). The median survival time (MST) of Group Ov (n = 9) was 45.4 months, and the OS at three years is 66.7% and 50.0% at five years. On the other hand, the MST of Group Ov+P (n = 8) was 9.3 months and the OS at three years was 0%. That is, the patients in Group Ov+P had significantly poorer prognoses than Group Ov (P = 0.029). RAS wild patients (n = 11) had a longer MST than RAS mutant patients (n = 3) (18.2 months vs. 13.7 months). The OS at three years of RAS wild patients was 44.4%, and 33.3% at five years. At one year, the OS of RAS mutant patients was 66.7%, and 0% at three years. The OS of RAS wild patients was longer than that of RAS mutant patients, but there was no statistical difference (P = 0.187).

Table 2 shows the results of the analysis of the clinicopathological characteristics of Group Ov and Group Meta. The median age of the patients in Group Ov was 52 years old, which was significantly younger than that of Group Meta (P = 0.003). There were 68 patients with liver metastases, 21 with lung metastases, and 19 with distant lymph node metastases in Group Meta. Fewer patients had lymph node metastases in Group Ov than in Group Meta (55.6% (5/9) vs. 90.0% (99/110), P = 0.003). The characteristics of patients and the serum CEA and CA19-9 levels were not significantly different between Group Ov and Group Meta. There were no postoperative complications that were more severe than Grade III, according to the Clavien-Dindo classification. All Group Ov patients underwent R0 resection, while in Group Meta, 43 patients underwent R0 resection, and 67 underwent R1 or R2 resection. The percentage of R0 resection procedures of Group Ov was significantly higher than Group Meta (100% (9/9) vs. 39.1% (43/110), P<0.005). Almost all patients in both groups received adjuvant chemotherapy (88.9% (8/9) and 83.6% (92/110), P = 0.679).

Table 2. Characteristics of Patients in Group Ov and Group Meta.

	Group Ov (n = 9)	Group Meta (n = 110)	*P* value
Age (median, years)	52 (42-79)	71 (40-95)	0.003
Location of primary tumor (right colon/left colon/rectum)	3/3/3	44/35/31	
Timing of metastasis (Synchronous/Metachronous)	7/2	47/63	0.229
Location of resection	Ovary: 9	Liver: 68 Lung: 21 Distant lymph node: 19 other: 2	
Regional Lymph node metastasis (-/+)	4/5	11/99	0.003
Histology (pap/tub/por/muc/unknown)	0/7/0/1/1	1/87/11/8/3	
CEA (median, ng/mL)	33 (1.2-629.4)	19 (1.2-39089)	0.781
CA19-9 (median, U/mL)	49 (2-458)	13 (2-2285)	0.507
Residual tumor classification (R0/R1, 2)	9/0	43/67	<0.005
Adjuvant chemotherapy (Yes/No)	8/1	92/18	0.679
Follow-up period (median, months)	33 (3-80)	21 (0-158)	

pap: papillary adenocarcinoma, tub: tubular adenocarcinoma, por: poorly differentiated adenocarcinoma, muc: mucinous adenocarcinoma, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

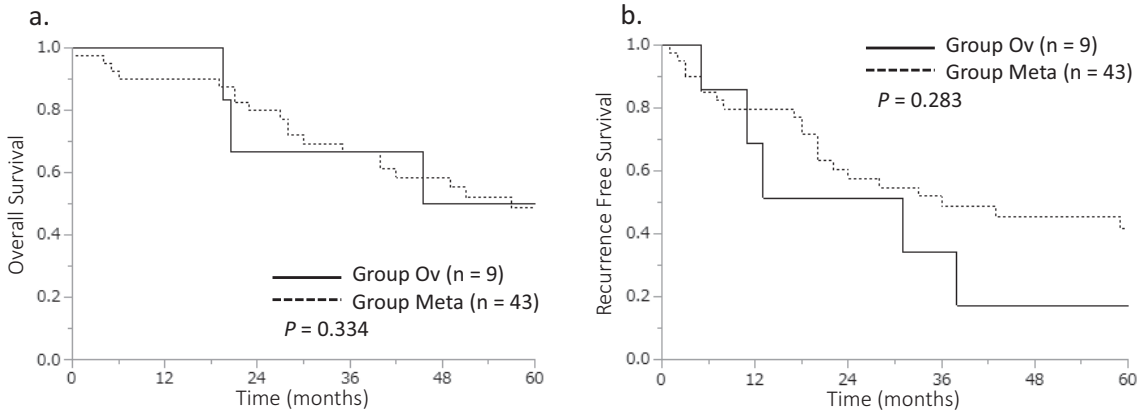

Figure 3. Kaplan-Meier curves of the overall survival a) and the recurrence-free survival b) of patients with R0 resection (Group Ov vs. Group Meta).
The prognosis was not significantly different between Group Ov and Group Meta.

Figure 3 shows OS curves and recurrence-free survival (RFS) curves for patients with only ovarian metastasis and a single distant metastasis who underwent R0 resection, according to the Kaplan-Meier technique. The MST of Group Ov (n = 9) was 45.4 months and the OS of three years was 66.7%, and 50.0% at five years. The MST of the 43 patients in Group Meta (n = 43) who underwent R0 resection was 53 months, and the survival time at three years was 66.7% and 48.7% at five years. There was no significant difference in prognosis (P = 0.334) (Figure 3a). The median RFS time of Group Ov was 13 months, and the three and five-year RFS rates were 31.4% and 17.4%. The median RFS time of Group Meta was 35.0 months, and the three and five-year RFS rates were 48.0% and 41.6%. There was also no significant difference (P = 0.283) (Figure 3b).

Discussion

Metastases to ovaries from CRC occur in 1.6%-6.4% of all female CRC patients. The risk factors of the onset of ovarian metastases from CRC reportedly include CRC before menopause, tumor invasion beyond T3, peritoneal metastases, and morphological abnormalities of the ovary[5]. The Japanese Classification of Colorectal Carcinoma and TMN classification classifies ovarian metastasis as distant metastasis. More specifically, in the previous edition of the Japanese Classification of Colorectal Carcinoma, ovarian metastasis from primary CRC was classified as P2, which

falls under limited metastasis to distant peritoneum. In the current 9th edition, metastasis to only the ovary without peritoneal metastases is classified as M1a, and ovarian metastasis with another distant metastasis or peritoneal metastases is classified as M1b or M1c2.

All ovarian metastases are associated with poor OS, even with resection of the metastatic sites; recently, however, there have been some reports showing opposite results. Fujiwara et al.[2] and Erroi et al.[3] reported that R0 resection of metastatic sites was associated with a significant increase in the survival time, and the five-year OS rate after R0 resection was 77.9%-80%. In our series, the five-year OS rate of Group Ov was 50%. Ovarian metastasis from primary CRC was previously classified under peritoneal metastasis and thought to be associated with a poor prognosis[5,6]. However, peritoneal metastasis is an adverse prognostic factor, and R0 resection of ovarian metastasis without peritoneal metastasis is associated with an increased OS time. Therefore, aggressive resection of ovarian metastases is associated with a good OS.

Previous reports have described the response rate of ovarian metastases to chemotherapy as 0%-5%, which is lower than that for other sites[7-9], and resection of large ovarian metastasis has improved symptoms such as abdominal pain, ileus, and abdominal distension[7]. As such, surgical resection seems to be an effective therapy. Regarding the surgical procedures for ovarian metastases, BSO is the most effective because of the high incidence of bilateral ovarian metastases and reports of metastases to the preserved ovary after USO. In the past, the incidence of bilateral ovaries reportedly ranged from 37%-75%[7]. In our 17 cases, 13 underwent BSO, and 4 underwent USO. After the pathological diagnoses, it turned out that seven of those 13 cases (54%) were bilateral metastases. Furthermore, during follow-up after USO, one of the four cases developed metastasis to the preserved ovary. One of the patients who underwent USO had resected an ovary before the diagnosis of ovarian metastasis, so USO was performed for ovarian metastasis. The reasons why USO was performed in three patients were unclear.

The pathway of ovarian metastasis from CRC remains unclear even though there are some hypotheses of direct dissemination from the primary CRC and through the lymphatics or blood vessels. About the pathway, Fujiyoshi et al.[10], Yamaguchi et al.[11], and Sato et al.[12] reported that lymphogeneous spread was important because many primary tumors contained lymphatic invasion shown in the histological examination. On the other hand, Graffner et al.[13] and Brinkrant et al.[14] suggested that hematogenous spread was important because of little flow between ovary and colon or rectum, and poor relationships between ovarian metastasis and regional lymphoid node metastasis. Fujiwara et al.[2] reported that the ovarian capsule was not invaded in almost cases. Hence, the hematogenous or lymphogeneous spread of malignant cells to the ovaries appears to be the most likely pathway. In our cases, peritoneal metastases were not detected in nine of 17 cases. Moreover, lymphatic invasion and venous invasion were detected from all 17 primary CRCs by histological examination. So, we speculated that the lymphogeneous or hematogenous spread of malignant cells to the ovaries appears to be the most likely pathway.

There are no chemotherapeutic regimens described in the guideline for administration after resection of the metastatic site. In our cases, almost all patients received adjuvant chemotherapy with Oxaliplatin.

The relationship between the RAS status and ovarian metastasis from primary CRC is largely unknown. Previous reports indicated that right-side colon carcinoma and an RAS mutation were associated with a poor prognoses[15-18]. In liver metastasis from primary CRC, a RAS mutation was an adverse prognosis factor[19]. In our cases, the MST of the 11 patients with RAS wild was longer than that of the three patients with RAS mutant, even though there was no significant difference. These findings that RAS mutation may be an adverse prognosis factor in patients with ovarian metastasis.

The most notable point of this study is that the five-year OS rate and RFS rate of the patients in Group Ov were not significantly different from those of the patients in Group Meta who received R0 resection in our institution. The published five-year survival rates after pulmonary metastasectomy range from 30.5% to 61.4%[20,21]. Regarding hepatic metastases, the five-year survival is reportedly 60% after hepatic metastasectomy[22]. These numbers mean that the prognosis after ovary metastasectomy is as long as that after surgery for pulmonary metastasis and hepatic metastasis when patients undergo R0 resection.

There are some limitations to this study. First, it was a retrospective study conducted at a single institution. Next, the number of patients with ovarian metastasis from CRCs was small. Finally, the follow-up period was not sufficient.

In conclusion, we found that the MST after surgical operation of patients with only ovarian metastases was significantly longer than that of patients with ovarian metastases and peritoneal metastases. Furthermore, when patients with ovarian metastases from CRC underwent R0 resection, a prognosis as good as that of female CRC patients with metastasis to one distant organ after R0 resection can be expected. This suggests that it is acceptable to classify ovarian metastasis as distant metastasis, rather than peritoneal metastasis, under the new definition.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

T.Y and N.S designed the study, and T.T, T.O, K.N, H.N,

M.H, Y.T, H.I, and K.D approved this study; T.Y and N.S and T.T and T.O performed colorectal cancer surgery in our hospital, and K.N, H.N, M.H, Y.T, H.I, and K.D assisted in their medical treatment. Within this study, T.Y and N.S, T.T, and O.T analyzed the data, and K.N, H.N, M.H, Y.T, H.I, K. D assessed the validity of that analysis; T.Y, N.S wrote the manuscript, and all author reviewed and edited the final manuscript.

Approval by Institutional Review Board (IRB)
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