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ORIGINAL ARTICLE

Comparison of long-term oncologic outcomes between metastatic ovarian carcinoma originating from gastrointestinal organs and advanced mucinous ovarian carcinoma

Hiroaki Kajiyama[1] · Shiro Suzuki[1] · Fumi Utsumi[2] · Nobuhisa Yoshikawa[1] · Kimihiro Nishino[1] · Yoshiki Ikeda[1] · Kaoru Niimi[1] · Eiko Yamamoto[1,3] · Michiyasu Kawai[4] · Kiyosumi Shibata[2] · Tetsuro Nagasaka[5] · Fumitaka Kikkawa[1]

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Abstract

Background Occasionally, ovarian tumors are found to have originated from non-ovarian organs as metastatic lesions since the ovary is a common site of metastasis from many cancers. The aim of the current study was to estimate the long-term oncologic outcome of patients with metastatic mucinous ovarian carcinoma (MmOC) in comparison with those with primary mucinous ovarian carcinoma (PmOC) at an advanced stage.

Materials and methods The data of one hundred and sixty-seven patients with mucinous ovarian cancer, including 91 patients with MmOC from the digestive organs and 76 patients with stage III–IV PmOC, were retrospectively analyzed. The prognostic significances of clinicopathologic factors were evaluated employing both uni- and multivariable analyses. Pathological slides were evaluated based on centralized pathological review.

Results The median age of patients with PmOC and MmOC was 55 (18–81) and 51 years (30–82), respectively. With follow-up of a total of 167 patients, 145 patients (86.8%) developed recurrence. In addition, 122 patients (73.0%) died of the disease. Regardless of the residual tumor status, patients with PmOC did not a show a significantly poorer OS than those with MmOC. Furthermore, in a Cox multivariable hazard model, after adjustment for various clinicopathologic confounders, a gastric cancer (GC)-originated tumor and larger residual tumor were significant predictors of poorer OS [GC (vs. PmOC): HR (95% CI) 2.205 (1.303–3.654), $P=0.0036$].

Conclusion The oncologic outcome of patients with MmOC was extremely poor; however, it was almost the same as that of those with PmOC. We should recognize MmOC derived from gastric carcinoma as a highly aggressive malignancy.

Keywords Metastatic ovarian carcinoma · Mucinous epithelial ovarian carcinoma · Overall survival · Residual tumor · Gastric carcinoma

✉ Hiroaki Kajiyama
kajiyama@med.nagoya-u.ac.jp

[1] Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan

[2] Department of Obstetrics and Gynecology, Bantane Hospital, Fujita Health University, Nagoya, Japan

[3] Department of Healthcare Administration, Graduate School of Medicine, Nagoya University, Nagoya, Japan

[4] Department of Obstetrics and Gynecology, Toyohashi Municipal Hospital, Toyohashi, Japan

[5] Department of Medical Technology, School of Health Science, Nagoya University Graduate School of Medicine, Nagoya, Japan

Abbreviations

PmOC	Primary mucinous ovarian carcinoma
MmOC	Metastatic mucinous ovarian carcinoma
WHO	World Health Organization
FIGO	International Federation of Gynecology and Obstetrics
OS	Overall survival
GC	Gastric carcinoma
CRC	Colorectal carcinoma

Introduction

Epithelial ovarian carcinoma (EOC) is one of the most lethal malignancies among cancers of the female reproductive system [1]. The presence of large ovarian masses is a

major finding in women with the disease. At present, a new generation of cytotoxic agents is being utilized in the clinical field of EOC. A number of chemotherapeutic agents, including bevacizumab combined with paclitaxel plus carboplatin, topotecan, and pegylated liposomal doxorubicin, are administered to women with EOC [2]. In addition, more appropriate surgical approaches and numerous supportive treatments have been implemented. The improved survival of EOC patients has been fully attributable to these systematic treatments.

However, these tumors can originate from non-ovarian organs as metastatic lesions since the ovary is a common site of metastasis from many cancers [3]. In mucinous pathology, we frequently encounter difficulty in distinguishing between primary mucinous EOC and metastasis from the digestive organs until obtaining definitive histological finding [4]. However, there is relatively little clinical information on metastatic ovarian carcinoma, and the oncologic outcome remains unclear. Furthermore, it remains unknown to what extent the long-term outcome of patients with metastatic ovarian carcinoma is poorer than that of those with other histological types.

Here, we focused on patients with metastatic mucinous ovarian carcinoma (MmOC) originating from the gastrointestinal organs, and overviewed the oncologic outcomes of patients with this tumor to investigate long-term overall survival, compared with patients with primary advanced mucinous epithelial ovarian carcinoma (PmOC).

Patients and methods

A total of 4413 patients with malignant ovarian neoplasm were registered between 1986 and 2015 by the Tokai Ovarian Tumor Study Group, consisting of Nagoya University Hospital and affiliated hospitals. Among these patients, there were 362 patients with FIGO I–IV mucinous ovarian cancer and 162 patients with metastatic ovarian cancer. In the current study, eligible cases for this registry system included those with: (1) centralized histological review by our referent pathologist with no knowledge of the patients' clinical data; (2) exclusion of borderline ovarian tumor; (3) available data on management and outcomes of patients. Data were collected from medical records and clinical follow-up visits. Patients were excluded from this study if they had insufficient clinical data or were lost to follow-up immediately after surgery. The stage was based on FIGO (International Federation of Gynecology and Obstetrics: 1988). The histological cell types were assigned according to the criteria of the World Health Organization (WHO). This study was approved by the ethics committee of Nagoya University. From the patients, we finally extracted 76 FIGO III–IV PmOC patients and 91 patients with MmOC from the gastrointestinal organs and pancreas. Patients with any histology except the mucinous type and tumors originating from other organs were excluded from this study.

To distinguish patients with primary and metastatic mucinous adenocarcinoma, under central pathological review, we adopted several referential criteria as follows [5]: (1) presence of segmental necrosis of tumoral glands that are characteristic of metastatic colorectal carcinoma, (2) presence of apparent signet ring cells (metastatic), (3) with or without a history of gastrointestinal carcinoma, and (4) in the majority of patients, immunohistochemical analysis, including cytokeratin (CK) 7, CK20, and CDX2, was conducted for routine diagnosis. An immunoprofile of CK7-positive/CK20-negative favored a primary ovarian tumor, while CK7-negative/CK20-positive suggested metastatic involvement.

Follow-up and analysis

At the end of the treatment, all patient follow-up was conducted at an outpatient clinic at each institution, every 1–3 months during the 1st–2nd year, every 3–6 months during the 3rd–5th years and annually thereafter. Follow-up procedures included gynecological examination, ultrasonographic scan, and serum CA-125. Evaluation with computed tomographic scan (CT) was repeated every 6–12 months during the first 2 years and once a year thereafter, or at the physician's discretion. Positron emission tomography (PET) was performed at the physician's discretion. The overall survival (OS) was defined as the time between the date of surgery and the last date of follow-up or death from any cause. The distributions of clinicopathologic events were evaluated using Student's *t* test and the Chi square test. Survival analysis was based on the Kaplan–Meier method. The survival curves were compared employing the log-rank test. All statistical analyses were performed with JMP Pro Ver.10.0 (SAS Institute Japan). A P value of < 0.05 was considered significant.

Results

Patients' characteristics

The patients' characteristics are summarized in Table 1. The median follow-up for surviving patients was 38.4 (1.0–174.0) months. The median age of patients with PmOC and MmOC was 55 (18–81) and 51 years (30–82), respectively. There was no difference in age distribution between the two groups ($P = 0.822$). Among the patients with PmOC, 55 patients (72.4%) had FIGO III disease, and 21 (27.6%) had IV disease. Original sites of the MmOC tumor were as follows: 32 (35.2%) in stomach (gastric carcinoma), 2

Table 1 Patient characteristics

	PmOC		MmOC		*P* value
	N	%	*N*	%	
Total	76		91		
Age					
Median (range)	55 (18–81)		51 (30–82)		0.8220[#1]
< 55	34	44.7	52	57.1	0.1102[#2]
≥ 55	42	55.3	39	42.9	
Tumor origin					< 0.0001
Ovary	76	100	0	0.0	
Gastric	0	0	32	35.2	
Colon	0	0	45	49.5	
Appendix	0	0	10	11.0	
Small intestine	0	0	2	2.2	
Rectal	0	0	1	1.1	
Cecum	0	0	1	1.1	
Residual tumor (cm)					< 0.0001
None	22	28.9	46	50.5	
< 2	33	43.4	16	17.6	
≥ 2	20	26.3	18	19.8	
NA	1	1.3	11	12.1	
Ascites volume (ml)					0.4051
None	7	9.2	12	13.2	
< 100	17	22.4	24	26.4	
100–499	17	22.4	23	25.3	
500–999	5	6.6	10	11.0	
≥ 1000	25	32.9	19	20.9	
NA	7	9.2	3	3.3	
Primary surgery					0.1263
TH + BSO ± OM + RPN	10	13.2	5	5.5	
TH + BSO ± OM + RPN + intestine[#3]	2	2.6	4	4.4	
TH + BSO ± OM	28	36.8	25	27.5	
TH + BSO ± OM + intestine[#3]	7	9.2	13	14.3	
TH + BSO ± OM + metastasectomy	0	0.0	2	2.2	
BSO ± OM	4	5.3	17	18.7	
BSO ± OM + intestine[#3]	2	2.6	2	2.2	
USO ± OM	10	13.2	9	9.9	
USO ± OM + intestine[#3]	1	1.3	5	5.5	
Other debulking	3	3.9	5	5.5	
Probe laparotomy	9	11.8	4	4.4	
Preoperative CA125 value (U/ml)					< 0.0001
≤ 35	67	88.2	50	54.9	
> 35	5	6.6	24	26.4	
NA	4	5.3	17	18.7	
Preoperative CA19-9 value (U/ml)					0.0123
≤ 37	47	61.8	36	39.6	
> 37	17	22.4	37	40.7	
NA	12	15.8	18	19.8	
Treatment period					0.5218
Before 1999	20	26.3	19	20.9	
2000–2004	15	19.7	15	16.5	
After 2005	41	53.9	57	62.6	

*CA*19-9 carbohydrate antigen 19-9, *TH* total hysterectomy (simple, semi-radical, and radical), *BSO* bilateral salpingo-oophorectomy, *USO* unilateral salpingo-oophorectomy, *OM* omentectomy, *RPN* retroperitoneal lymphadenectomy, *#1* Student *t*-test, *#2* Chi-squared test, *#3* resection of intestine, including small intestine, colon, and appendix

(2.2%) in small intestine, 45 (49.5%) in colon, 10 (11.0%) in appendix, 1 (1.1%) in rectum, and 1 (1.1%) in cecum. In addition, the rates of the presence of a residual tumor (RT) were higher in the PmOC group than in the MmOC group ($P<0.0001$). The distribution of the surgery type did not differ between the groups ($P=0.1263$).

Overall survival of patients with PmOC and MmOC

With follow-up of a total of 167 patients, 145 patients (86.8%) developed recurrence. In addition, 122 patients (73.0%) died of the disease. Recurrent disease was noted in 71 (93.4%) patients with PmOC and 74 (81.3%) patients with MmOC. Death was noted in 64 (84.2%) patients with PmOC and 58 (63.7%) patients with MmOC. The 3-year and 5-year OS rates of patients with PmOC were 29.2, and 23.3%, respectively. In addition, those of patients with MmOC were 28.4 and 19.2%, respectively. Figure 1 shows the OS curves of PmOC and MmOC patients. Patients with PmOC did not show a significantly poorer OS than those with MmOC ($P=0.6089$). Moreover, based on patients' characteristics, the distribution of RT differed between the two groups. Thus, we next stratified patients according to the RT status. In the presence of RT less than 2 cm in diameter at the initial surgery, there was no difference in the OS between patients with MmOC and PmOC ($P=0.5896$) (Fig. 2). Likewise, in patients with RT larger than or equal to 2 cm in diameter at initial surgery, the survival of patients of both groups tended to be similar ($P=0.9272$) (Fig. 3). On stratification by absent or present RT, similarly, we did not identify any significant difference in OS between the two groups [Fig. 4a: absent RT ($P=0.0929$), Fig. 4b: present RT ($P=0.3694$). On the other hand, confining analysis to each histological cohort (PmOC and MmOC), the RT status was a significant prognostic factor for OS (RT < 2 cm (or absent) vs. ≥ 2 cm: $P=0.0107$ (Fig. 5a: PmOC), $P=0.0301$ (Fig. 5a: MmOC).

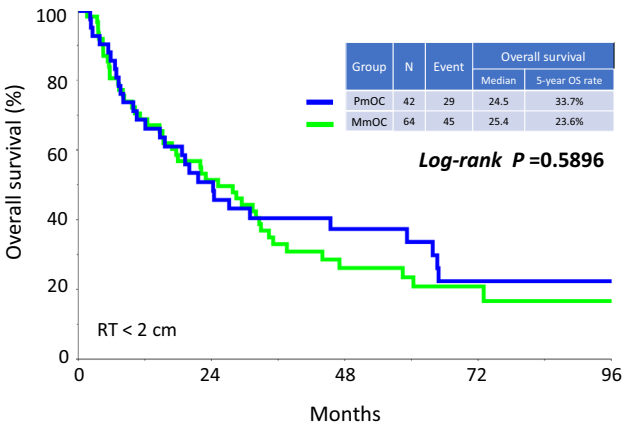

Fig. 2 Kaplan–Meier estimated survival of patients with < 2 cm (or absent) residual tumor (log-rank: $P=0.5896$)

We subsequently stratified patients according to the metastatic origin, including gastric carcinoma (GC) and colorectal carcinoma (CRC). Among a total of 32 patients with GC-derived MmOC, 29 patients (90.6%) developed recurrence, and 26 patients (81.2%) died of the disease within the observational follow-up duration. On the other hand, in patients with non-GC, 45 (76.3%) developed recurrence and 38 (64.4%) died of the disease. The median OS times of patients with GC and non-GC MmOC were 8.1 and 28.1 months, respectively. The OS of patients with GC was significantly poorer than that of those with non-GC MmOC ($P=0.0019$) (Fig. 6). Furthermore, in the Cox multivariable hazard model, after adjustment for various confounders, including the age, tumor origin, size of RT, and volume of ascites, a GC-originated tumor and larger residual tumor were significant predictors of poorer OS [GC (vs. PmOC): HR (95% CI) 2.205 (1.303–3.654), $P=0.0036$, presence of ≥ 2 cm residual tumor (vs. < 2 cm or

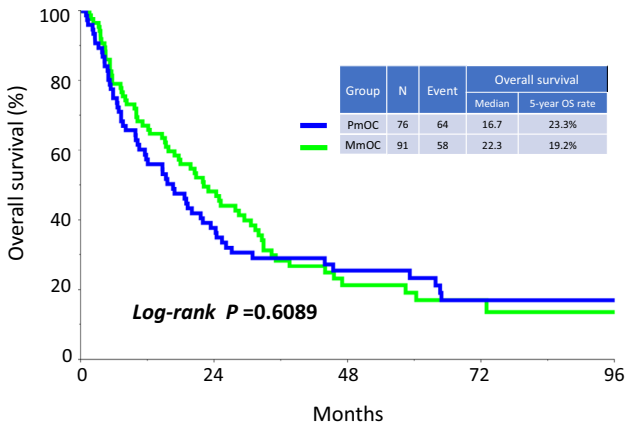

Fig. 1 Kaplan–Meier estimated overall survival (OS) of patients with PmOC and MmOC (log-rank: $P=0.6089$)

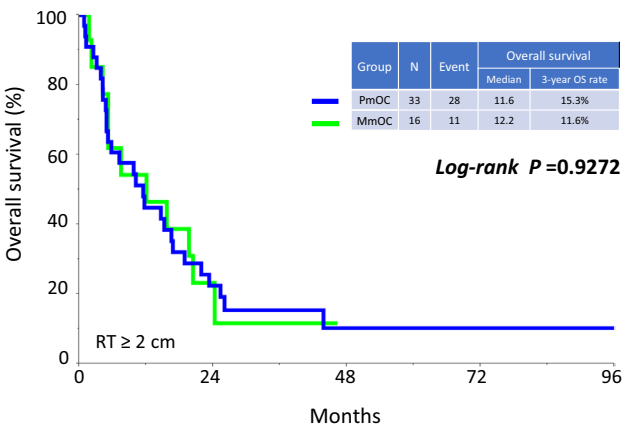

Fig. 3 Kaplan–Meier estimated survival of patients with ≥ 2 cm residual tumor (log-rank: $P=0.9272$)

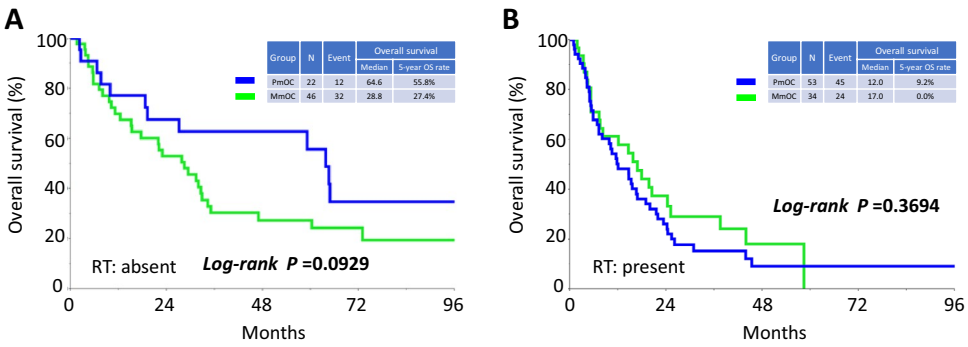

Fig. 4 **a** Kaplan–Meier estimated survival of patients without (absent) residual tumor (Log-rank: $P=0.0929$). **b** Kaplan–Meier estimated survival of patients with (present) residual tumor (log-rank: $P=0.3694$)

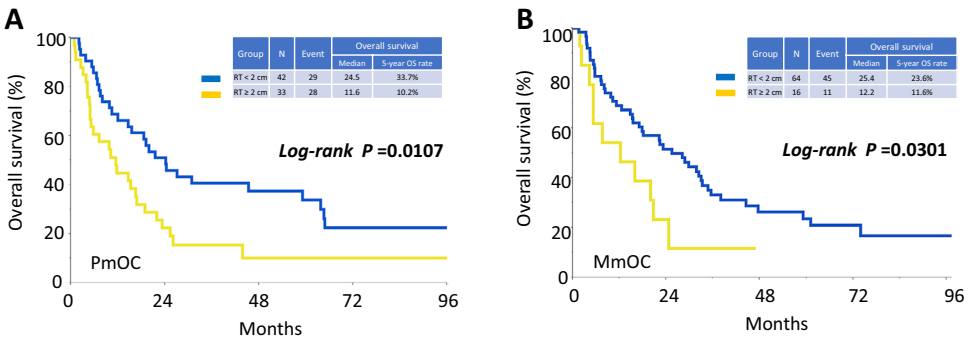

Fig. 5 **a** Kaplan–Meier estimated survival of PmOC patients with < 2 cm (or absent) residual tumor (Log-rank: $P=0.0107$). **b** Kaplan–Meier estimated survival of MmOC patients with ≥ 2 cm residual tumor residual tumor (log-rank: $P=0.0301$)

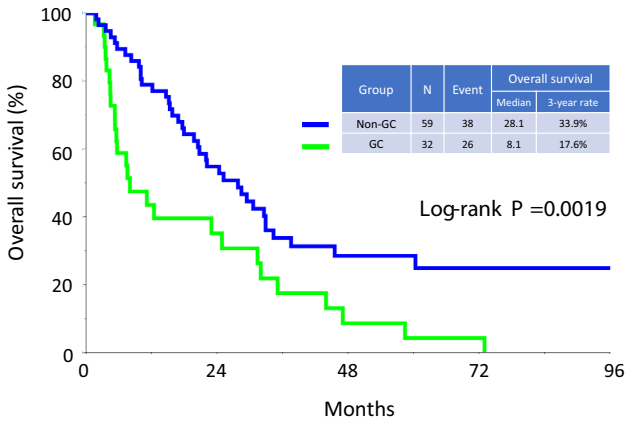

Fig. 6 Kaplan–Meier estimated survival of patients stratified by the tumor origin. The OS of patients with GC was significantly better than that of those with non-GC MmOC ($P=0.0019$)

none): HR (95% CI) 2.022 (1.309–3.094), $P=0.0017$]. However, patients with non-GC MmOC did not show poorer OS than those with PmOC [non-GC (vs. PmOC): HR (95% CI) 0.776 (0.492–1.207), $P=0.2636$] (Table 2).

Table 2 Multivariable Cox hazard model of overall survival

	Overall survival		
	HR	95% CI	*P* value
Age			
< 55	Referent		
≥ 55	1.089	0.752–1.577	0.6480
Tumor origin			
PmOC	Referent		
GC	2.205	1.303–3.654	0.0036
Non-GC	0.776	0.492–1.207	0.2636
Residual tumor			
< 2 cm or absent	Referent		
≥ 2 cm	2.022	1.309–3.094	0.0017
NA	1.364	0.607–2.739	0.4285
Ascites volume (ml)			
0/< 100	Referent		
≥ 100	1.667	1.121–2.513	0.0113
NA	1.566	0.521–3.822	0.3908

HR hazard ratio, *95% CI* 95% confidence interval, *GC* gastric carcinoma

Discussion

The hallmarks of ovarian carcinoma are so complicated that it is difficult to understand the diverse biological behavior of this tumor. PmOC is basically an uncommon subset of EOC. According to an earlier study, the incidence of PmOC was approximately 12% as exemplified by a recent population-based study derived from the SEER database in which 11.9% of 40,571 women were diagnosed with EOC between 1988 and 2007 [6]. According to prior studies, advanced-stage PmOC was highly lethal, with patients showing markedly

poorer survival than women with the serous histological type [7, 8]. Regarding the long-term oncologic outcome, Hess et al. reported that the median overall survival was 12.0 and 36.7 months ($P<0.001$) in mucinous and non-mucinous ovarian carcinoma patients, respectively [7]. In the present study, 71 (93.4%) patients with PmOC finally developed recurrence and 64 (84.2%) patients with PmOC died of the disease. Additionally, the 5-year OS rate of patients with PmOC was 23.4%. The markedly poorer oncologic outcome in this study was consistent with previous reports. This poor outcome was reported to be based on the fact that patients with PmOC show a significantly weaker response to first-line platinum-based chemotherapy compared with patients with other types of ovarian carcinoma. Actually, in a retrospective analysis, on comparing 47 patients with advanced-stage PmOC and 94 with serous carcinoma treated with the same protocols, the overall response rates were 38.5% (95% CI 23.4–55.4%) and 70% (95% CI 58.5–80.3%), respectively, for serous carcinoma ($P=0.001$) [9]. In addition, in a Japanese multi-institutional study enrolling 64 patients with PmOC, the response rate to chemotherapy in PmOC patients was significantly lower than for serous carcinoma patients (12.5 vs. 67.7%, respectively) [10]. Taken together, we re-realized that advanced-stage PmOC patients exhibited a marked recurrence/mortality risk, and that this tumor is considered a separate entity. Therefore, we are hopeful for positive results from large-scale prospective studies on additional treatments for this tumor.

Malignant ovarian neoplasms are also occasionally found as metastatic lesions from extra-ovarian organs because the ovary is somehow a common site of metastasis from a variety of cancers. In fact, it is very difficult to estimate the accurate incidence of metastatic ovarian carcinoma due to the different methods of pathological assessment and analysis. In addition, there is also a wide geographical variation in the incidence of common gastric, breast, and colorectal carcinomas as well as changing incidences in many population groups over recent decades [4]. Indeed, about 4% of women with carcinoma from the gastrointestinal tract showed a risk of ovarian metastasis during the course of their disease [11–13]. According to our recent study using centralized pathological review, among 3478 patients with malignant ovarian cancer, a total of 143 (4.1%) patients had metastatic ovarian carcinomas with a median age of 54 (29–82) years. The most and second most frequent original tumors were colorectal (43%, $N=62$) and gastric (29%, $N=42$) carcinoma, respectively [14]. In the present study, our primary question was whether an accurate diagnosis promotes the appropriate selection of chemotherapy, leading to a better oncologic outcome. Actually, the standard chemotherapeutic agents for patients with PmOC and colorectal mucinous carcinomas are individually defined as the taxane plus platinum combination and fluoropyrimidines, respectively. In our work, we demonstrated that the long-term clinical outcomes of patients with both types of mucinous carcinoma were extremely poor (5-year OS rates: PmOC: 23.4%, MmOC: 19.2%). In addition, the comparison between the two pathological groups revealed no difference in overall survival. We subsequently examined whether the RT status influenced the difference in oncologic outcomes, since its distribution was different between the two cohorts. However, irrespective of the presence or absence of RT larger than or equal to 2 cm in diameter at the initial surgery, there was no difference in the OS between patients with MmOC and PmOC ($P=0.9979$). Thus, these results suggest that the outcomes of women categorized as having MmOC compared with advanced PmOC differed little, regardless of the RT status.

In the present study, we showed that among patients with GC-derived MmOC, 91.0% of patients developed recurrence, and 81.2% of patients died of the disease within the observational follow-up duration. In addition, the oncologic outcome of patients with GC was significantly poorer than that of those with non-GC MmOC or PmOC (Fig. 4, Table 2). According to prior reports, the prognosis associated with metastatic ovarian carcinoma originating from GC is extremely poor. Based on a retrospective study analyzing a total of 54 patients with Krukenberg tumors of the ovary, 5-year survival rates after resection of primary lesions in the stomach, colon, rectum, and breast were 0, 20.7, and 22.2%, respectively [15]. In another study comparing the mean survival time between 111 patients with GC- and 45 patients with colorectal-originated metastatic ovarian carcinoma, survivals of women with a colorectal origin was significantly longer than that of those with a gastric origin [16]. In this context, these results are in agreement with earlier data. Needless to say, complete resection of the tumor is important; however, those patients will experience recurrence at a high rate despite such surgical efforts. Indeed, recurrence essentially arises from occult metastases that were not successfully removed by various treatments or the body's immune system. Based on the present results, the effect of postoperative chemotherapy on GC patients is thought to be limited. We should recognize such GC-derived MmOC as a highly aggressive malignancy, to be considered as an entirely different entity in clinical practice.

Our current work still includes several limitations. Initially, because the present study was essentially retrospective, many factors relevant to the treatment decision were not strictly controlled. Subsequently, the composition of the study subjects may have been influenced by referral bias owing to its multicentric design over a long-term study period. Furthermore, one of the major weaknesses of the current study was lack of detailed information about adjuvant chemotherapy in patients with MmOC. On the other hand, one of the strengths of our current work was the centralized pathological review by expert pathologists in gynecologic

malignancy. It is a big challenge to discriminate PmOC from secondary ovarian carcinoma from primary extra-ovarian sites, including the stomach, pancreas, and colorectal areas. Actually, Zaino et al. reported that the reviewing of pathological slides and reports of PmOC by three independent pathologists resulted in reclassification of the majority (57 to 63%) of mucinous carcinomas as metastatic to the ovary rather than the ovary being the primary site [8]. As well as microscopic hallmarks, immunohistochemical staining pattern of cytokeratins 7 and 20 (CK7/20) can be useful to distinguish PmOC and MmOC from gastrointestinal tract tumors [17, 18]. In the almost universally CK7-negative metastases of lower gastrointestinal tract origin, coordinate expressions of CDX2 (83%) and cytokeratin 20 (86%) were equivalent. CDX2 was comparable to CK20 in distinguishing metastases of lower gastrointestinal tract origin (CK7-negative and CDX2/CK20-positive) from primary ovarian tumors and metastases of upper gastrointestinal tract origin (CK7-positive and CDX2/CK20-variable) [19]. This reassessment system enabled us to accomplish unified evaluation of the discrimination of both types of mucinous tumors, contributing to appropriate diagnosis and reduced intraobserver variability.

In conclusion, the ovary is a frequent site of metastasis from many cancers, although the detailed mechanism is yet to be elucidated. Despite the fact that the incidence of MmOC is very low, we should keep in mind that the origin of MmOC, particularly from colorectal and gastric cancer, should be considered when encountering ovarian cancer to ensure the appropriate clinical management of patients by an expert physician.

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Author contribution HK: data analysis and interpretation, writing manuscript, SS, FU, YI, KN, KN, MK, and NY: data collection, TN: pathological evaluation, KS: supervisor of this work, FK: supervising and funding.

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Compliance with ethical standards

Conflict of interests The authors have nothing to disclose.

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