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Original Article

Difficulty in diagnosis and different prognoses between colorectal cancer with ovarian metastasis and advanced ovarian cancer: An empirical study of different surgical adoptions

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ABSTRACT

Objective: To determine the clinical manifestations and optimal management of female patients with advanced colorectal cancer (CRC) metastasis in ovaries mimicking advanced ovarian malignancy.
Materials and Methods: A retrospective medical records review of female patients with primary CRC metastasis to ovaries, which were initially diagnosed as ovarian malignancy, and treated between 2001 and 2013. Clinical presentations, pathologic findings, and treatment outcomes were analyzed.
Results: In total, 19 cases were collected in the study through a hospital tumor registry. The mean age of the patients at the time of diagnosis was 45 years (range, 28–63 years). The most common symptoms were abdominal pain or increased abdominal girth (63%). None of them had rectal bleeding. The ratio of cancer antigen-125 to carcinoembryonic antigen was available in 13 out 19 patients (less than 25 in 76.9%). Barium enema or colonoscopic exam was only performed in 10 outpatients. None of them had a positive finding. All 19 patients went for surgery, all of them had ovarian metastasis but only eight of them had bilateral involvement, and 14 of them had carcinomatosis. All patients went for either optimal cytoreduction surgery or suboptimal cytoreduction surgery. The patients who received optimal cytoreduction surgery had a significant better progression-free and overall survival than those who did not.
Conclusion: Clinical manifestations of primary CRC with ovarian metastasis may be confused with advanced ovarian cancer. Negative barium enema or colonoscopic exam cannot rule out the possibility of CRC. For patients with a cancer antigen-125 to carcinoembryonic antigen ratio less than 25, 76% are good reference of CRC metastasis to ovaries. Optimal cytoreduction surgery like that used for treating advanced ovarian cancer had a better prognosis than suboptimal cytoreduction colorectal cancer treatment.

Introduction

Ovaries are not an unusual site for cancer metastasis. However, colorectal cancer (CRC) is the most common cancer metastatic to ovaries [1,2]. The incidence of ovarian metastasis was between 4% and 30.8% of primary CRC found in previous studies [1,2]. Metastatic ovarian tumor can be discovered as an adnexal mass in a patient with a prior history of colon cancer and this metachronous recurrence is more likely to be accurately diagnosed before surgery. It has been reported that 2% of the patients with primary CRC develop metachronous ovarian metastases within 2 years after primary resection [3]. Otherwise, CRC with synchronous ovarian metastasis are often discovered at the time of surgery as advanced ovarian cancer by a gynecologic oncologist. In order to give the right preoperative diagnosis and appropriate management, we review those

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clinical features, laboratory data, and treatment prognosis difference in order to provide better management.

Materials and methods

After Institutional Review Board approval, the medical records of patients with primary CRC which was diagnosed initially as ovarian cancer and treated at the study center from 2001 to 2013 were retrospectively reviewed. A total of 2191 female patients with primary CRC were diagnosed in this period. Among them, 91 patients (4.15%) with ovarian metastasis were diagnosed, including 65 patients with synchronous (2.97%) and 26 patients with metachronous (1.19%) ovarian metastasis. Among these 91 patients, 19 patients with ovarian metastasis were diagnosed as primary ovarian cancer before surgery.

The patients' characteristics, symptoms, image studies, preoperative serum carcinoembryonic antigen (CEA) and cancer abtigen-125 (CA-125) values, stage of disease, ovarian involvement, and type of surgical treatment were collected for analysis. Optimal cytoreductive surgery was defined as "less than 1 cm of residual disease remaining after surgery." Progression-free survival (PFS) and overall survival (OS) were defined as the interval from the date of diagnosis to the first evidence of progression and disease-specific death, respectively. Progression of the disease was defined as image findings and/or persistent elevation of tumor markers. PFS and OS were estimated using the Kaplan–Meier method and compared using a log-rank test. All statistical analyses were performed using SPSS software for Windows, version 19 (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered to indicate statistical significance.

Results

Nineteen female patients, who met the previously described conditions, were identified. The mean age of patients was 45 years (range, 28–63 years). The most common presenting symptoms were abdominal pain or increased abdominal girth (63%). Five of them (26.3%) presented as acute abdomen with suspected tumor rupture and emergent exploratory laparotomy was performed under the impression of suspected ovarian cancer. Only three patients had gastrointestinal tract symptoms. Two patients complained of poor appetite and one had diarrhea. Two patients were pregnant at the time of diagnosis (Table 1). One of them was found to have a pelvic mass at prenatal examination by ultrasonography. Preoperative barium enema or colonoscopic examination was only administered to 10 patients (52%). All of them were negative but one patient was suspected of having possible rectal cancer. This patient received emergent exploratory laparotomy due to acute abdomen. The preoperative image study is shown in Table 2. Pretreatment serum CEA and CA-125 were available for 15 patients and the values were elevated (>5 U/mL) in 14 patients (93.3%) and (>35 U/mL) in 12 patients (80%). The ratio of CA-125/CEA was available for 13 patients, demonstrating a ratio of ≤25 in 10 patients (76.9%; Table 1). Initial surgery was performed by a gynecologic oncologist in all cases. A frozen section was elicited in 16 patients and metastatic tumors were suspected in only seven patients (43.8%). The report from the frozen sections was as follows: colon cancer: one case; appendiceal mucinous adenocarcinoma: one case; suspected metastatic adenocarcinoma: five cases; endometrioid adenocarcinoma: four cases; mucinous adenocarcinoma: two cases; adenocarcinoma: two cases; and borderline tumor: one case (Table 3).

During surgery, nine had optimal cytoreduction (residual tumor ≤1 cm in maximal diameter) and the other 10 patients had suboptimal surgery. After a complete pathologic study, the location of primary cancer in this study was as follows: rectum: six cases, sigmoid colon: six cases; ascending colon: two cases; hepatic flexure colon: one case; descending colon: one case; cecum: one case; and appendix: two cases (Table 3). At the time of surgery, five patients had isolated ovarian metastasis. Among these five patients, three had pelvic lymph node metastasis. For the other 14 patients, 13 had carcinomatosis and one had pulmonary metastasis. These patients all underwent salpingooophorectomy with or without hysterectomy, debulking of metastatic tumors, and colorectal surgery according to the operative finding (Table 3).

Postoperative chemotherapy was offered to all patients, most commonly with a combination of 5-fluourouracil and leukovorin monthly for 6 months.

All patients had ovarian involvement but five patients had confined metastasis to the ovaries. They had a median overall survival time of 28 months (range,15–51 months) compared with 16 months (range, 3–58 months).

Table 1
Clinical findings of patients with ovarian metastasis. CA-125 = cancer antigen-125; CEA = carcinoembryonic antigen.

No.	Age (y)	Gravida	Para	CEA	CA-125	CA-125/CEA	Symptom	Special condition
1	57	5	4	518	268	0.51	Abdominal distention Diarrhea	
2	44	6	3	5.84	52.2	8.9	Abdominal pain	Acute abdomen
3	36	2	1	15.3	785	51	Pelvic mass during prenatal exam	Pregnancy 22 wk
4	39	3	2	—	—		Abdominal pain	Acute abdomen
5	33	0	0	—	173		Poor appetite Body weight loss	
6	45	2	2	12.3	31	2.52	Abdominal pain	
7	31	2	2	24	302	12.5	Abdominal distension	
8	41	1	0	16.7	15.2	0.91	Vaginal bleeding	Acute abdomen
9	34	?	?	29.6	—		Abdominal pain	Acute abdomen
10	55	4	3	10.2	38.29	3.74	Abdominal pain	
11	63	6	3	164	190	1.15	Abdominal distension Poor appetite	
12	36	4	0	—	146.2		Abdominal pain	Pregnancy 35 wk
13	51	2	2	15.4	—		Abdominal pain	Acute abdomen
14	45	3	2	—	—		Abdominal fullness	
15	59	5	5	11.9	499.5	42	Abdominal pain	
16	54	6	4	31.4	105.7	3.3	Abdominal fullness	
17	28	0	0	4.43	626.7	141.4	Abdominal mass	
18	55	7	4	17.1	9.6	0.56	Abdominal mass	
19	57	2	2	64.9	578.7	8.91	Abdominal pain	

Table 2
Preoperative image study of patients with ovarian metastasis.

No.	CT scan or MRI				GI survey
	Description	Ascites	Carcinomatosis	Size (cm)	
1	Multiple pelvic complex masses R/O Ovarian cancer	Moderate	Present	3 × 5	Barium enema: external compression
2	Pelvic mass, R/O ovarian cancer Retroperitoneal LN metastasis	Nil	Nil	5 × 4	Barium enema: external compression Colonoscopy: normal
3	(MRI) Pelvic solid mass	Nil	Nil	12 × 9	Nil
4	Ill-defined pelvic mass	Nil	Nil	5 × 6	Nil
5	Right ovarian tumor	Nil	Present	8 × 10	Barium enema: external compression
6	NA			11 × 8 (by sono)	Barium enema: external compression
7	Pelvic mass, ovarian malignant tumor R/O A-colon mass or metastasis	Mild	Nil	32 × 24	Barium enema: external compression
8	Ovarian tumor rupture	Mild	Nil	8 × 5	Nil
9	Pelvic mass	Massive	Nil	18 × 15	Nil
10	Pelvic mass, r/o ovarian cancer	Nil	Nil	15 × 15	Nil
11	Pelvic mass, r/o ovarian cancer Wall thickening of D-colon	Massive	Present	10 × 9	Barium enema: external compression
12	NA			16 × 13 (by sono)	Nil
13	Pelvic mass with tumor rupture	Massive	Nil	10 × 9	Barium enema: external compression Colonoscopy: normal
14	Pelvic mass, r/o ovarian cancer	Mild	Nil	18 × 13	Nil
15	Pelvic mass	Massive	Present	6 × 5	Colonoscopy: normal
16	Pelvic mass with carinomatosis	Massive	Present	16 × 14	Barium enema: external compression
17	Pelvic mass	Massive	Nil	12 × 8	Nil
18	Pelvic mass, r/o ovarian cancer	Mild	Nil	21 × 14	Colonoscopy: normal
19	Pelvic mass, r/o ovarian cancer	Massive	Nil	14 × 12	Nil

CT = computed tomography; GI = gastrointestinal; LN = lymph node; MRI = magnetic resonance imaging; NA = not applicable.

Patients who received optimal cytoreduction had a significant better median of PFS after surgery (21 months, range 8–39) when compared with patients who had suboptimally cytoreduction surgery (3 months, range, 0.5–16, $p < 0.05$; Figure 1). Patients with optimal cytoreduction were also associated with a significantly longer median of OS (56 months, range, 15–58) when compared with patients with suboptimally cytoreduction surgery (16 months, range 3–48, $p < 0.05$; Figure 2).

Discussion

In the present study, we found that clinical features of primary CRC with ovarian metastasis may be confused with those of advanced ovarian cancer. Primary CRC with ovarian metastasis is not rare; the reported incidences vary from 5% to 31% in autopsy data and 0% to 8.6% in clinical series [1,4]. Omranipour and Abasahl [4] reported a low incidence of CRC with synchronous and metachronous ovarian metastases (2.7% and 6.6%, respectively). Isolated ovarian metastases from primary CRC occurred in 3.3% of women undergoing colorectal resection. The high incidences of peritoneal diseases, transmural tumor extension, and lymphatic diseases were noted in their series. They suggest that the lymphatic pathway and direct peritoneal dissemination via transmural extension should be important mechanisms of ovarian involvement in CRC [4]. Similarly, we found that 12 patients (63.2%) in the study had lymph node involvement and 13 patients (68.4%) presented with carcinomatosis. Under these circumstances, tumors were less likely to grow as a submucosal lesion. This could be the reason why no patient in our study experienced typical bloody stool and no patient had a positive barium enema study.

A protein known as CEA is commonly secreted by CRC patients. In the present study, 93.3% of patients had elevated CEA. However, the CEA values in patients with inflammatory diseases overlap those of patients with benign and/or malignant tumors of the gastrointestinal tract and of other sites which include breast, bronchus, urothelium, ovary, uterus, and cervix. Therefore, CEA cannot be used independently to establish a diagnosis of CRC. It has been reported that using CA-125/CEA ratio appeared to be more excellent than CEA alone for differentiation between patients with ovarian cancer and nonovarian cancers [5,6]. A sensitivity of 91% and a specificity of 100% for detection of ovarian cancer has been reported by using the CA-125/CEA ratio with value exceeding 25 [7]. When considering CA-125/CEA ratio, 76.9% (10/13) of our patients has the ratio of CA-125/CEA less than 25. CEA is not a typical marker for ovarian cancer and most primary CRC with definitive diagnosis do not check the marker of CA-125. After surveying our cases in the same study period, we found that 80% (28/35) have the ratio of CA-125/CEA less than 25 in our patients in confirmed primary CRC and there are 27.9% (111/154) with the ratio of CA-125/CEA less than 25 in our patients in confirmed primary ovarian cancer. It may be one of the clues for suspect metastatic ovarian malignancy. Some recent studies revealed that human epididymis protein 4 is superior to CA-125 in distinguishing a benign ovarian tumor from primary ovarian malignancies [8]. Whether human epididymis protein 4 can be used to identify primary ovarian cancer or metastatic tumor might need further evaluation.

It still remains controversial whether colon screening should be considered as a part of preoperative workup for gynecologic oncologic patients. Saltzman et al [9] have concluded that colon screening is not needed in the asymptomatic patient with age below 50 years old, but a full colonoscopy should be considered for those older than 70 years. In our study, nine cases did not receive colon survey due to the following reasons: emergent surgery in three, pregnancy in two, and physicians' preference in four. Ten cases had received colon survey by barium enema examination and two of them had additional colonoscopic studies. All results showed external compression of pelvic mass. Interestingly, two cases with normal barium enema and colonoscopy had primary appendiceal cancer with ovarian metastasis. Appendiceal carcinoma is rare and usually not diagnosed prior to surgery [10]. A study by Dietich 3rd et al [11] revealed that only two out of 48 patients with CRC had the diagnosis of appendiceal cancer prior to surgery. Although the sensitivity of colonoscopy for the diagnosis of CRC (95%) was greater than that of the barium enema (82.9%) [12], CRC with scirrhous or lateral tumor spreading type (Figure 3) is still

Table 3
Surgical findings of patients with ovarian metastasis.

No.	Surgery	Ascites	Frozen section	Final pathology	Primary site	Ovarian metastasis	Lymph node metastasis	Optimal surgery	Radicality[a]
1	ATH+BSO+BPLN+ omentectomy Appendectomy+Hartmann's operation		Mucinous adenocarcinoma	Mucinous adenocarcinoma	Rectum	Right	No	Suboptimal	R2
2	SATH+BSO T-loop colostomy		Adenocarcinoma, suspect metastasis	Adenocarcinoma	S-colon	Bilateral	No	Suboptimal	R2
3	BSO+omentectomy High AR with colonic anastomosis+ T-loop colostomy	1600 cc	Endometrioid adenocarcinoma	M-D Adenocarcinoma	S-colon	Bilateral	Yes	Optimal	R2
4	ATH+LSO Hartmann's operation	3000 cc	Metastatic adenocarcinoma	M-D Adenocarcinoma	Rectum	Left	Yes	Suboptimal	R2
5	RSO Hartmann's operation		Endometrioid adenocarcinoma	M-D Adenocarcinoma	Rectum	Right	Yes	Optimal	R2
6	ATH+BSO+BPLN+appendectomy+ omentectomy+hemicolectomy		Adenocarcinoma, suspect metastasis	M-D Adenocarcinoma	Cecum	Right	Yes	Optimal	R0
7	BSO Right hemicolectomy	250 cc	Adenocarcinoa, suspect metastasis	Mucinous adenocarcinoma	A-colon	Bilateral	Yes	Suboptimal	R2
8	ATH+BSO+BPLN+omentectomy Left hemicolectomy	100 cc	Endometrioid adenocarcinoma	M-D Adenocarcinoma	S-colon	Right	Yes	Optimal	R0
9	RSO+omentectomy Radical proctectomy	2500 cc	Borderline tumor	M-D Adenocarcinoma	Rectum	Right	No	Optimal	R0
10	ATH+BSO+BPLN+omentectomy Left hemicolectomy		Metastatic adenocarcinoma	M-D Adenocarcinoma	S-colon	Bilateral	Yes	Suboptimal	R1
11	ATH+BSO+BPLN+omentectomy Left hemicolectomy	4200 cc	Endometrioid adenocarcinoma	M-D Adenocarcinoma	D-colon	Left	No	Suboptimal	R2
12	C/S, RSO+omentectomy Right hemicolectomy		Borderline mucinous tumor	M-D Adenocarcinoma	A-colon	Right	Yes	Suboptimal	R2
13	RSO	2300 cc	nil	M-D Adenocarcinoma	Rectum	Right	Yes	Optimal	R1
14	BSO+BPLN+omentectomy right hemicolectomy	200 cc	Adenocarcinoa	M-D Adenocarcinoma	T-colon	Bilateral	Yes	Optimal	R2
15	BSO Loop ileostomy	3500 cc	nil	Mucinous adenocarcinoma	S-colon	Bilateral	No	Suboptimal	R2
16	ATH+BSO+BPLN+appendectomy +omentectomy+left hemicolectomy	3500 cc	nil	Mucinous adenocarcinoma	Appendix	Bilateral	No	Suboptimal	R2
17	RSO Sigmoid colectomy	2100 cc	Metastatic adenocarcinoma	M-D Adenocarcinoma	S-colon	Right	Yes	Optimal	R0
18	BSO+omentectomy appendectomy right hemicolectomy		Appendiceal mucinous adenocarcinoma	Mucinous adenocarcinoma	Appendix	Bilateral	No	Optimal	R0
19	ATH+BSO+BPLN+appendectomy+ omentectomy+proctectomy	3000 cc	Adenocarcinoma	P-D Adenocarcinoma	Rectum	Left	Yes	Suboptimal	R1

ATH = abdominal total hysterectomy; BSO = bilateral salpingo-oophorectomy; BPLN = bilateral pelvic lymphadenectomy; LSO = left salpingo-oophorectomy; M-D = moderately differentiated; P-D = poorly differentiated.; RSO = right salpingo-oophorectomy; SATH = subtotal abdominal hysterectomy.

[a] Radicality was assessed according to operative record by proctologist.

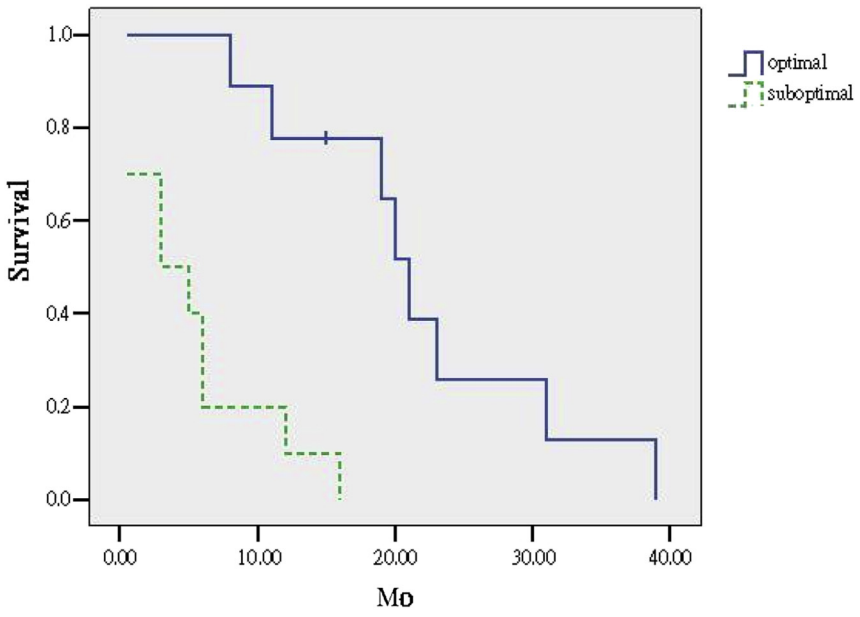

Figure 1. Progression-free survival for women with optimal (median 21 months, range 8–39 months, $n = 9$) versus suboptimally cytoreduction (median 3 months, range 0.5–16 months, $n = 10$, $p = 0.004$).

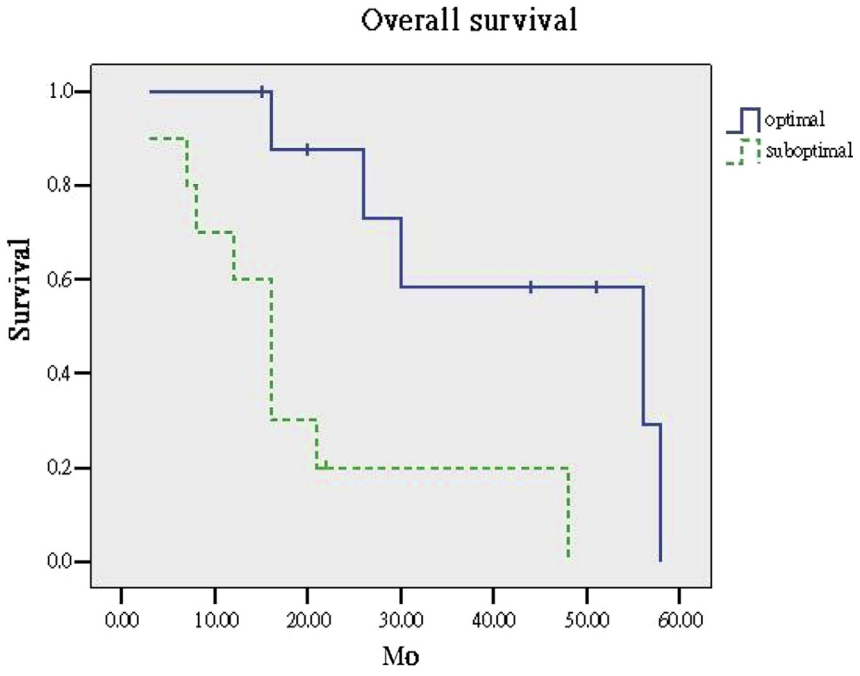

Figure 2. Overall survival for women with optimal (median 56 months, range 15–58 months, $n = 9$) versus suboptimally cytoreduction (median 16 months, range 3–48 months, $n = 10$, $p = 0.004$).

more likely to be missed by colonoscopy. In our study, incomplete study of colonoscopy due to obstruction by carcinomatosis with peritoneal seeding made preoperative diagnosis difficult.

The role of frozen sections in distinguishing between primary and secondary ovarian malignancy is important because the surgical management of primary and secondary neoplasia differs significantly. However, it was difficult to differentiate the gastrointestinal from the ovarian origin of neoplasia. Stewart et al [13] reports that 58.8% of metastatic ovarian malignancies would be correctly identified on frozen sections. They conclude that poorly differentiated high-grade serous carcinomas, primary endometrioid, and mucinous adenocarcinoma were more difficult to be distinguished from primary ovarian malignancy and metastasis from a CRC. Similar findings were noted in our study, which revealed that seven patients (43.8%) had a suspect frozen diagnosis of metastatic ovarian malignancy. The remaining cases comprised endometrioid adenocarcinoma and mucinous tumor in frozen sections. Bilateral ovarian involvement was also mentioned as an indicator for possible metastatic tumor origin [13]. Our results supported these viewpoints because eight of 19 (42.1%) cases had bilateral disease. Since it is difficult to have a definitive diagnosis during surgery in some cases, all ovarian malignancies with

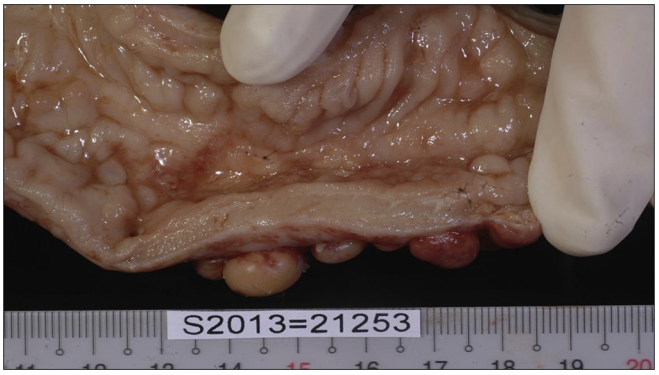

Figure 3. Scirrhous type colorectal cancer is more likely to be missed by colonoscopy.

uncertain diagnosis or with colon invasion should undergo appropriate surgical staging with bowel resection.

Previous reports conclude that female patients with isolated ovarian metastases have a better prognosis than those with diffuse pelvic metastasis and a significant survival advantage is to be offered optimal cytoreduction [2,14]. In our study, patients with isolated ovarian metastasis have a trend towards better OS but the trend has not reached statistical significance. In these five patients with isolated ovarian metastasis, three had lymph node metastasis. This may be the reason for compromised clinical outcome. In this study, we also found that patients who received optimal cytoreduction experienced better PFS and OS. We also analyzed our total 91 cases of primary CRC of ovarian metastasis and showed a better OS (52 vs. 11 months, $p < 0.05$) in patients with optimal cytoreduction. The definition of optimal cytoreduction surgery for primary ovarian cancer was residual tumor less than 1 cm. In primary CRC, the radicality of the surgical procedure performed was classified as "curative" (R0, no tumor left behind microscopically at resection margins); "questionably curative" (R1, tumor left behind microscopically at resection margins, or any other "Gray zone" situation that would question a curative operation, such as suspect but unproven metastases); "palliative" (R2, macroscopical tumour left behind); or "unresectable." It shares the same concept of aggressive cytoreduction for primary ovarian cancer or CRC [15]. In the report by Andreoni et al [15], there are marked differences in OS rates in R0, R1+R2, and unresectable patients (82%, 35%, and 0% respectively, $p < 0.0001$). As describe by McCormick et al [2], they use the definition of optimal cytoreduction (residual $\leq$ 1 cm) in primary CRC with ovarian metastasis and concluded optimal cytoreduction was associated with better PFS and OS.

Given the recent improvement in chemotherapies and target therapy for CRC, these observations suggest a role of optimal debulking surgery as it does in the management of ovarian cancer.

Standard treatment for patients with epithelial ovarian cancer was cytoreductive surgery followed by adjuvant chemotherapy. However, some selected patients with clinically-apparent, unresectable disease may receive neoadjuvant chemotherapy prior to definitive surgery. In these patients, CRC with ovarian metastasis should be taken into the differential diagnosis. Ojo et al [16] pointed out the factors for misdiagnosis including: lack of history of gastrointestinal symptoms, abdominal distension, elevated CA-125 levels, and outside reports in support of ovarian primary. Our study suggested that the factors leading to difficult preoperative diagnosis include scirrhous or lateral tumor spreading-type tumor, primary appendiceal origin, presence of acute abdomen [17], and association with pregnancy.

In our study, two cases were diagnosed during pregnancy. Malignant adnexal masses in pregnancy are responsible for approximately 3% of all ovarian tumors [18]. There seems to be an increasing incidence for acute presentation in pregnancy. The diagnosis and treatment also seem to be a big challenge. Symptoms of CRC including abdominal pain, nausea, anemia, and rectal bleeding are usually masked by pregnancy and would lead to late diagnosis of the disease and a subsequently poor prognosis [19]. The prognosis of pregnancy with metastatic ovarian cancer still remains poor.

In summary, our results demonstrated that clinical features of primary CRC with ovarian metastasis may be confused with those of advanced ovarian cancer. Negative findings of barium enemas or even colonoscopic examinations cannot exclude the possibilities of CRC. For patients with a CA-125/CEA ratio less than 25, a diagnosis of ovarian metastasis from CRC should be considered. Optimal cytoreduction is associated with better PFS and OS. A multi-center study with larger scale is warranted for clarification.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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