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Hepatic resection for recurrent metastatic ovarian carcinoma or peritoneal carcinoma: a retrospective case-control study

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Summary

Purpose of investigation: This study was performed to investigate the validity of hepatic resection as a treatment option for hepatic parenchymal metastasis in patients with recurrent epithelial ovarian carcinoma or primary peritoneal carcinoma. *Materials and Methods:* A retrospective case–control study was conducted. Fisher's exact test and Kaplan–Meier analysis were used to analyze the clinicopathologic characteristics and survival of 40 patients with hepatic parenchymal metastasis from recurrent ovarian carcinoma or primary peritoneal carcinoma. *Results:* Of these 40 patients, 12 characterized by unilobar metastasis underwent hepatic resection as part of secondary cytoreductive surgery, while 28 underwent only salvage chemotherapy. The median overall survival time from the time of the liver metastasis was significantly longer in patients who underwent hepatic resection as part of secondary cytoreduction than those who underwent salvage chemotherapy (62 *vs*. 14 months, respectively; $p = 0.04$). *Conclusion:* Hepatic resection has the potential to improve survival for patients with hepatic parenchymal metastasis from recurrent ovarian carcinoma or primary peritoneal carcinoma.

Key words: Hepatic resection; Ovarian carcinoma; Recurrence; Survival.

Introduction

Epithelial ovarian cancer is a leading cause of gynecologic malignancies worldwide. Cytoreductive surgery followed by platinum- and paclitaxel-based chemotherapy is currently the most widely accepted standard treatment for advanced-stage ovarian carcinoma [1, 2]. Despite the achievement of complete clinical remission after the initial treatment in more than 50% of patients [3], relapse still occurs in most of these patients [4, 5]. Treatment of recurrent ovarian carcinoma, especially that involved liver metastases, is more difficult than treatment of primary disease.

With the development of therapy for liver metastasis from colorectal carcinoma and neuroendocrine tumors, liver resection has been proven to be a practicable treatment method with lower morbidity and mortality rates and improved survival [6-9]. Patients with Stage IV ovarian cancer may reportedly experience prolonged survival following hepatic resection involving primary cytoreduction [10, 11]. Moreover, hepatic resection for recurrent metastatic ovarian carcinoma is safe and might offer a survival advantage for patients with isolated liver metastases [12-16]. However, the indications for and advantages of hepatic resection for treatment of metastatic ovarian carcinoma or primary peritoneal carcinoma remains largely unclear. It is critical to identify the characteristics of patients who would benefit more from hepatic resection as part of a secondary cytoreductive procedure than from systemic therapy.

In this retrospective case–control study, the effects of treatment were compared between secondary cytoreduction with liver resection and systemic therapy in patients with liver metastases of ovarian carcinoma or primary peritoneal carcinoma.

Materials and Methods

The study was approved by the Research Ethics Committee of Peking University Cancer Hospital & Institute (2016KT39). Informed consent was obtained from all individual participants included in the study.

The authors identified 151 consecutive patients who were diagnosed with recurrent epithelial ovarian carcinoma or primary peritoneal carcinoma at Peking University Cancer Hospital & Institute from November 1996 to December 2015. Among them, 40 patients with liver metastases at the time of recurrence were registered and retrospectively reviewed. All patients had subsequently received a median of six cycles (range, 1–10) of platinum-based chemotherapy following the primary surgical management. The patients' clinicopathologic characteristics were retrospectively collected from the medical, surgical, and pathologic records and reviewed. Liver metastases were evaluated by two radiologists based on both hepatic ultrasound examination and abdominal CT.

The following clinical features were obtained from the medical

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records in Beijing Cancer Hospital with follow-up visits: tumor characteristics, primary therapy, platinum-free interval, cancer antigen 125 (CA125) level, intraoperative and postoperative events, chemotherapy before and after hepatic resection, and the patients' follow-up status.

Before surgery, the hepatobiliary surgeons discussed the resectability of the hepatic metastases according to the CT findings for all patients with recurrent tumors. All hepatic resections were performed by hepatobiliary surgeons. The positions of the hepatic metastases were directly confirmed by palpation or indirectly confirmed by intraoperative ultrasound examination. The excision margin of the metastatic lesions was ≥ 1 cm. The types of liver resections performed were segmentectomy and simple hepatic metastasis resection. Optimal cytoreduction was defined as surgery with an extrahepatic and hepatic residual tumor measuring ≤ 2 cm in its greatest diameter.

Patients with recurrence-related disease and unresectable liver metastases (>10 liver metastases or extrahepatic disease) were treated with systemic therapy, which involved intravenous platinum-based chemotherapy: paclitaxel at 175 mg/m^2 and carboplatin according to an area under the curve of 5 to 6 (using the Calvert formula) [17], cyclophosphamide at 600 mg/m^2, doxorubicin at 50 to 60 mg/m^2 and cisplatin at 60 to 70 mg/m^2 or cyclophosphamide at 600 mg/m^2, and cisplatin at 60 to 70 mg/m^2 or carboplatin according to an area under the curve of 5 to 6. The second-line chemotherapy drugs included liposomal doxorubicin, docetaxel, gemcitabine, topotecan, 5-fluorouracil, and oxaliplatin.

Statistical analyses were performed using SPSS). Data were analyzed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Kaplan–Meier analysis was used to calculate survival curves and rates, and their differences were evaluated using the log-rank test. All tests with a p-value of < 0.05 were considered statistically significant.

Results

The patients' characteristics are summarized in Table 1. Twelve (30.0%) patients underwent liver resection as part of secondary cytoreduction. The remaining 28 patients underwent systemic chemotherapy without liver resection. Several differences in clinicopathologic characteristics were observed between the liver resection group and systemic chemotherapy group. First, the liver metastases were most commonly located in the left lobar region in the liver resection group and in the right lobar or bilobar region in the systemic chemotherapy group ($p = 0.012$). Second, significantly fewer patients had more than three liver metastases in the liver resection group than in the systemic chemotherapy group ($p = 0.003$). Finally, the median platinum-free interval prior to recurrence was much longer in the liver resection group than in the systemic chemotherapy group (27 *vs*. 10 months, respectively; $p = 0.038$). There were no significant differences between the two groups in the other clinical characteristics, including the patients' age, tumor histology, tumor grade, residual disease at the time of the primary diagnosis, or CA125 level at the time of recurrence with liver metastases ($p > 0.05$) (Table 1).

The detailed clinicopathologic characteristics of the 12 patients with recurrent tumors who underwent liver resection are shown in Table 2.

The main type of liver resection was segmentectomy in ten (83.3%) patients; the other two patients underwent partial liver metastasis resection. At the time of liver resection, six patients underwent cytoreduction of extrahepatic metastases including pelvic mass dissection, partial gastrectomy, small bowel mesenteric mass resection, partial diaphragm resection, and splenectomy. Liver resection with clear resection margins was achieved in nine out of ten patients who underwent segmentectomy. The other three patients underwent suboptimal surgery with residual liver disease.

The median operative time was 150 (range, 45–270) minutes, median estimated blood loss was 250 (range, 50–2000) ml, median blood transfusion volume was 0 (range, 0–1200) ml, and median post-resection hospital stay was 12 (range, 8–19) days. Two patients were transferred to the intensive care unit upon completion of the secondary cytoreduction. No intraoperative or postoperative deaths occurred, and complications developed in three patients (superficial wound dehiscence, arrhythmia, and reactive pleural effusion, respectively). Nine patients underwent six cycles (range, 1–13) of chemotherapy after hepatic resection until disease progression occurred. Three patients refused to undergo chemotherapy after surgery.

The median follow-up duration for the cohort was 48.5 (range, 8–125) months. Seven of the nine patients who underwent liver resection with clear hepatic margins developed hepatic relapse. Six of these patients developed relapses in the original recurrent position of the liver, and one patient developed a simultaneous relapse in the pelvis. The last patient developed bilobar relapse (Table 3).

The median overall survival time for the cohort was 63 (95% confidence interval [CI], 35–91) months, and the cumulative five-year overall survival rate was 51.8%. The median progression-free interval and median overall survival time for all patients after the development of liver metastasis were nine (95% CI, 4–14) months and 20 (95% CI, 7–33) months, respectively. The median overall survival time was analyzed to determine the prognostic roles of variables that have been previously suggested as potential prognostic factors for hepatic resection of recurrent metastatic ovarian carcinoma or primary peritoneal carcinoma. The statistically significant factors that were correlated with improved survival were a greater than a six-month disease-free interval after primary therapy ($p = 0.001$), unilobar liver metastasis ($p = 0.012$), and fewer than three liver metastases ($p = 0.003$) (Table 3).

The median overall survival time after liver metastasis for patients who underwent optimal secondary cytoreduction was 62 (95% CI, 0–133) months, and that in patients who underwent systemic chemotherapy it was 14 (95% CI, 9–19) months. The three-year overall survival rate after liver metastasis was significantly higher in the patients who underwent optimal secondary cytoreduction than in those who underwent systemic chemotherapy (66.7% *vs*. 18.5%, respectively; $p = 0.004$) (Figure 1).

Table 1. — *Characteristics of 40 patients with hepatic metastases.*

Characteristic	Patients who had secondary cytoreduction including hepatic resection (n=12)	Patients who had only salvage chemotherapy (n=28)	*p* value
Stage (FIGO)			0.443
I	3	2	
II	1	3	
III	6	19	
IV	2	4	
Histologic subtype			0.780
Serous	8	20	
Clear cell	1	2	
Endometrioid	1	1	
Mixed	0	1	
Transitional cell	0	1	
Mucinous	0	1	
Primary peritoneal carcinoma	2	2	
Tumor grade			0.132
G2-3	11	20	
Unknown	1	8	
Primary cytoreductive outcome			0.806
≤ 2cm	9	22	
> 2cm	3	6	
Median age in years at hepatic metastasis (range)	59.9 (43-70)	60 (41-78)	0.572
Site of hepatic metastasis			0.012[a]
Left lobar	3	4	
S2	1	0	
S3	1	0	
Other	1	4	
Right lobar	9	14	
S6	7	8	
S7	2	3	
Other	0	3	
Bilobar	0	10	
Median size of hepatic metastasis in cm (range)	3.1(1.5-18)	2.3(0.6~6.6)	0.050
No. of hepatic metastasis			0.003[a]
1	10	11	
2	2	2	
≥ 3	0	15	
Site of tumor metastasis			0.263
Hepatic metastasis	3	3	
With extra hepatic metastasis	9	25	
Median level of CA125 with hepatic metastasis in u/ml (range)	159.5 (16-550)	241.1 (50-5000)	0.182
Median disease free interval in months (range)	27(7-57)	10(2-85)	0.038[a]

FIGO: International Federation of Gynecology and Obstetrics; CA125: cancer antigen 125. [a]Significant with p < 0.05.

Discussion

In this study, 40 patients with recurrent ovarian carcinoma or primary peritoneal carcinoma who developed hepatic parenchymal metastasis were treated with liver resection or systemic therapy. Hepatobiliary surgeons determined the most appropriate treatment method according to each patient's CT images. The results of this case–control study suggest that patients with resectable liver lesions have a significantly longer overall survival after surgery than do patients who undergo systemic therapy only. The current study indicates that surgery is the preferred treatment for patients with liver metastasis from recurrent ovarian carcinoma or primary peritoneal carcinoma.

In 1983, Berek *et al.* [18] first introduced the term "secondary cytoreduction," which is defined as repeated tumor-reductive operations for recurrent ovarian cancer. Although, the potential utility of secondary cytoreduction has re-

Table 2. — *Characteristics of 12 patients with hepatic resection.*

Case	Age	Stage (FIGO)	Pathologic type of primary disease	Grade of primary disease	Residual disease of primary cytoreduction	Platinum free interval (months)	Chemotherapies before hepatic resection (cycles)	Position of hepatic metastasis	Number of hepatic metastasis	Size of hepatic metastasis, largest diameter (cm)	Extrahepatic metastasis	Residual disease of secondary cytoreduction	Recurrence in the liver after hepatic resection (months)	Survival after hepatic metastsis (months)	Overall survival (months)
1	62	IIa	Serous papillary adenocarcinoma	G2	< 2 cm	36	0	S7	1	5.3	None	None	16	62	98
2	70	IIIc	Primary peritoneal carcinoma	G3	> 2 cm	10	7	S6	1	14.5	Mesentery of sigmoid colon	None	6	26	59
3	62	IIIc	Serous papillary adenocarcinoma	G3	< 2 cm	12	1	S3	2	1.8	Para-aortic lymph node	< 2 cm	11	25	36
4	46	IIIc	Primary peritoneal carcinoma	G3	< 2 cm	7	6	S6	1	6.6	Peritoneum of pelvis or abdomen	> 2 cm	Residual	12	25
5	63	IIIc	Serous papillary adenocarcinoma	G3	> 2 cm	40	10	S2	1	2.9	Antrum of stomach	None	24	75	121
6	58	IIIc	Serous papillary adenocarcinoma	G2	< 2 cm	30	27	S6	1	2.0	None	None	-	76	118
7	57	IIIc	Serous papillary adenocarcinoma	G3	< 2 cm	42	1	S3,S4	2	2.7	Abdominal peritoneum and mesentery of small bowl	< 2 cm	12	20	79
8	44	Ic	Clear cell carcinoma	G3	0	22	3	S6	1	3.0	Diaphragm	None	5	27	56
9	57	IIIc	Serous papillary adenocarcinoma	G2	< 2 cm	14	2	S6	1	6.0	Peritoneum of pelvic and Para-aortic lymph node	> 2 cm	-	15	43
10	64	IIIc	Serous papillary adenocarcinoma	G3	> 2 cm	24	6	S6	1	18.0	Spleen and Para-aortic lymph node	> 2 cm	Residual	9	86
11	61	Ia	Serous papillary adenocarcinoma	G3	0	57	6	S7	1	3.3	None	None	-	18	81
12	43	Ic	Endometrioid carcinoma	Unknown	0	56	8	S6	1	2.5	Spleen, peritoneum of pelvis	< 2 cm	3	14	78

Table 3. — *Survival of 40 patients after hepatic metastasis from recurrent ovarian carcinoma or primary peritoneal carcinoma according to clinicopathologic variables*

Variable	Median survival (months)	*p* value (log rank)
Age at hepatic metastasis (years)		NS
< 60	14.5	
≥ 60	13.5	
Primary cytoreductive outcome (cm)		NS
≤ 2	18.5	
> 2	12.0	
Primary tumor grade		NS
2	13.5	
3	14.5	
Primary histologic subtype		NS
Serous	15.5	
Other	12.0	
Stage		NS
I/II	18.0	
III/IV	13.0	
Disease free interval after primary therapy (months)		0.001
≤ 6	26.0	
> 6	12.0	
Site of liver metastasis		0.012
Unilobar	26.0	
Bilobar	12.0	
No. of liver metastasis		0.003
< 3	31.0	
≥ 3	12.0	
Diameter of largest liver metastasis (cm)		NS
< 5	14.5	
≥ 5	12.0	
Extrahepatic metastasis		NS
With	13.0	
Without	40.0	

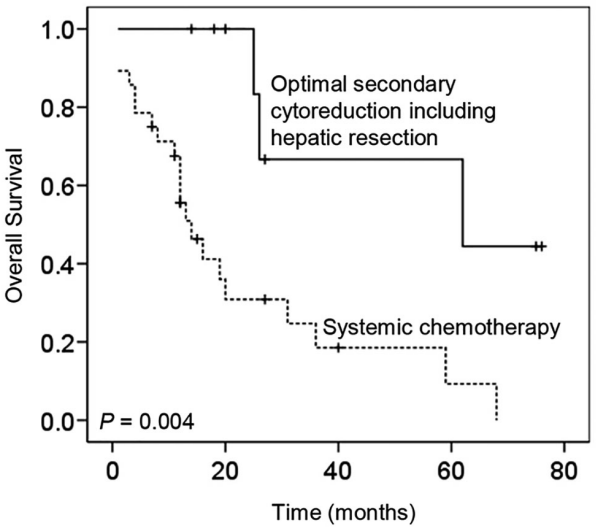

Figure 1. — Survival curves for patients who underwent optimal secondary cytoreduction including hepatic resection and salvage chemotherapy after the development of liver metastasis (p = 0.004).

mained controversial throughout the last two decades, it is widely accepted that secondary cytoreduction is feasible and can prolong the survival of patients with recurrent ovarian cancer. One study showed that such patients will benefit from secondary cytoreduction with a disease-free interval of more than six to 12 months from the completion of primary therapy [5].

Liver metastasis of ovarian cancer mostly originates from peritoneal seeding (versus hematogenously) [10], develops slowly [14], recurs later without symptoms, and with concurrent metastasis at other sites [19, 20]. In the present study, 34 (85.0%) patients had concurrent metastasis, and only six had simple hepatic metastasis. In contrast to primary hepatic cancer, hepatic metastases in patients with recurrent epithelial ovarian carcinoma or primary peritoneal carcinoma are often located at the surface or under the envelopment of the liver with a clear borderline. Thus, partial liver resection or segmental resection instead of more extensive liver lobectomy is usually required [21]. No perioperative mortality occurred in the present study. Acceptable complications developed in three of 12 patients. Therefore, consistent with previous studies [13, 14, 19, 21], hepatic resection was found to be safe and acceptable for the patients in the present cohort with recurrent ovarian cancer.

Previous studies have supported the survival advantage of hepatic resection for colorectal and neuroendocrine tumors. Although the presence of recurrence at other sites simultaneously with hepatic metastasis from ovarian cancer is associated with a poor prognosis [20], Scarabelli *et al.* [22] found that secondary cytoreductive surgery including partial liver resection improved survival of patients with recurrent ovarian cancer with a recurrence-free survival duration of 13 to 24 months. The present study involved a 13-year retrospective review of a single institution's experience with therapy for recurrent metastatic ovarian cancer or peritoneum cancer. Similar to previous reports by Yoon *et al.* [19], Abood *et al.* [14], and Kolev *et al.* [23], who indicated that hepatic resection along with resection of other gross disease could prolong the survival of patients, the present authors found that survival after the development of hepatic metastasis in patients who underwent optimal surgery including hepatic resection was significantly better than that in patients treated only with systemic therapy (median overall survival 62 *vs*. 14 months; three-year cumulative survival rate, 66.7% *vs*. 18.5%, respectively). Thus, hepatic resection as a part of optimal secondary cytoreduction should be considered as a treatment option in selected patients with recurrent ovarian or peritoneal cancer.

Several criteria are used to select which patients with re-

current ovarian cancer will likely benefit from liver resection [5, 13, 14, 19, 20, 23]. These criteria include fewer than three liver metastases, a metastasis located in one segment, or one lobe of the liver, and a platinum-free interval of greater than six months. Consistent with previous studies, the present authors avoided hepatic resection in patients who would have been left with suboptimal debulking. Because liver resection is not appropriate for all patients with metastatic ovarian cancer, more stringent criteria will continue to be developed for appropriate selection of patients.

This study had some limitations. First, on an ethical basis, a randomized clinical trial to compare liver resection with systemic therapy in patients with liver metastasis cannot be performed. Thus, a case–control study is the next best alternative for comparison of these two treatment strategies in patients with liver metastasis from recurrent ovarian carcinoma or peritoneal carcinoma. Second, the number of patients was small. Further studies including more patients are required to fully evaluate the role of liver resection in patients with recurrent ovarian cancer with liver metastasis.

Conclusion

The present study has demonstrated that hepatic resection for liver metastases from recurrent ovarian cancer or peritoneal cancer has the potential to improve the long-term survival of patients who have undergone optimal secondary cytoreduction surgery. Although a larger cohort analysis and longer-term follow-up are required to identify other prognostic factors associated with improved outcomes, hepatic resection should be considered as an alternative option for the treatment of liver metastasis in patients with recurrent ovarian carcinoma or peritoneal carcinoma.

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