Treatment of liver metastases in patients with epithelial ovarian cancer

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To the Editor: The liver is one of the most vulnerable organs of metastatic tumors. A metastatic tumor of the liver is about 18 to 40 times more common than a primary liver tumor (LM). There are approximately 50,000 new ovarian cancer patients in China each year, and the annual mortality rate is approximately 40%.[1] At present, the treatment for LM in malignant tumors includes surgical treatment and nonsurgical treatment. Nonsurgical treatment mainly includes systemic chemotherapy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), etc.

Our study retrospectively analyzed the curative effect and prognosis of liver metastases in 43 patients with epithelial ovarian cancer (EOC) who were treated at Peking University People's Hospital between January 2013 and July 2018. All patients were followed up until June 2019 or until they were lost to follow-up. All patients received systemic chemotherapy. The medical ethics committee of Peking University People's Hospital approval was obtained for this retrospective study (No. 2019-105).

Oligometastasis was defined as the number of LMs ≤ 5, and nonoligometastasis was defined as the number of LMs > 5.[2] LMs found at the time of diagnosis of the primary tumor or before diagnosis were defined as simultaneous LMs, while LMs found after surgery were defined as metachronous metastases.[3]

Data analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). The Kaplan–Meier method was used to calculate the survival curve, and a univariate analysis was performed. Cox regression analysis was performed on the statistically significant factors in the univariate analysis to calculate the independent prognostic factors of OS. $P < 0.05$ indicates statistical significance.

The general clinical data of 43 patients are shown in Table 1, with a median age of 54 years. A total of three patients had LM in the left lobe of the liver, 35 patients had LM in the right lobe of the liver, and five patients had bilobular involvement. The average diameter of the metastases was 2.7 ± 1.2 (range: 1.0–5.3) cm.

Among the 17 patients with simultaneous LMs, 14 received local resection of LMs (82.4%, 14/17) and the remaining three received RFA (17.6%, 3/17). Among the 26 patients with metachronous LMs, 13 received hepatectomy (50.0%, 13/26), 11 received RFA (42.3%, 11/26), and the remaining two received TACE (7.7%, 2/26).

The median progression-free survival was 11 months, the 5-year OS rate was 36.5%, and the median OS time was 24.6 months. There was a significant difference in survival between the oligometastasis and nonoligometastasis groups ($P = 0.033$).

The maximum diameter of metastasis was 3 cm, and the survival difference between the two groups was statistically significant ($P = 0.038$). There was also a statistically significant difference in survival with three LMs treatment (hepatectomy, RFA, and TACE), with OS times of 28.6, 19.3, and 9.5 months, respectively ($P = 0.026$). There was no significant difference in age, pathological type, time of metastasis diagnosis, or the location of metastasis.

Five patients underwent BRCA testing, including three patients who received hepatectomy, two cases with BRCA mutation, and two cases underwent RFA, one with BRCA mutation. The OS of the two was 29.4 and 23.4 months, respectively. But statistical analysis was not performed because of the small number of cases (Supplementary Figure 1, http://links.lww.com/CM9/A441).

The single-factor analysis of prognosis showed statistically significant differences in OS according to the size of residual lesions, tumor grade, number of LMs, maximum diameter of LMs, and treatment procedure. In the multifactor analysis, the size of residual lesions represented

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Table 1: General information of 43 patients with liver metastases from ovarian cancer.

Characteristics	Patients (*n*)	Median survival time (months)	*P* values
Age			0.662
≤60 years	28	25.3	
>60 years	15	22.6	
Residual tumor lesion			0.032
≤1 cm	31	25.5	
>1 cm	12	13.4	
Histologic subtype			0.073
Serous	33	28.4	
Nonserous	10	22.4	
Tumor grade			0.048
Low	7	19.7	
High	36	28.3	
Stage (FIGO)			0.074
I–II	4	28.4	
III–IV	39	20.5	
Detection time of metastases			0.502
Simultaneous	17	27.4	
Metachronous	26	21.6	
No. of liver metastases			0.033
Oligometastasis	40	26.6	
Nonoligometastasis	3	12.2	
Maximum diameter of LM			0.038
≤3 cm	25	27.3	
>3 cm	18	18.8	
Site of liver metastases			0.770
Unilobular	38	25.8	
Bilobular	5	23.5	
Treatment procedure			0.026
Hepatectomy	27	28.6	
RFA	14	19.3	
TACE	2	9.5	

FIGO: International Federation of Gynecology and Obstetrics; LM: Liver tumor; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization.

a combination of the number and diameter of LMs, so it was excluded. The Cox regression analysis showed that the number of LMs > 5, a maximum diameter of LM > 3 cm, and the treatment procedure are independent factors affecting prognosis.

Approximately 75% of EOC were diagnosed at an advanced stage, and 12% to 33% diagnosed at stage IV.[4] Therefore, early diagnosis and standardized treatment are of great clinical significance in the treatment for LM of EOC.

It has been reported that among all treatment methods, hepatectomy results in the longest survival of patients. Some scholars have adopted the definition of oligometastasis and believe that more than five metastases should be considered unresectable. In our study, 40 patients had oligometastasis, 27 received surgical resection, and 13 received RFA. The OS of patients who received surgical resection were higher than that of the patients who received RFA (28.6 months *vs.* 19.3 months).

For patients with advanced EOC, optimal cytoreduction is the key factor affecting prognosis. The prognosis of recurrent EOC depends mainly on the location, size, and chemosensitivity of the recurrent tumor, such as whether the relatively isolated and resectable tumor can achieve optimal cytoreduction, and other factors can significantly improve patient prognosis.[5] In our study, 27 patients underwent optimal cytoreduction includes hepatectomy, the OS time was 25.5 months, and 13.4 months in patients who received suboptimal cytoreduction includes hepatectomy. This result suggests that hepatectomy with optimal cytoreduction can prolong the total survival period and improve the prognosis of patients LM of EOC.

Patients with unresectable LMs usually accept nonsurgical treatment, includes systemic chemotherapy, RFA, TACE, *etc*. RFA is usually used as an effective supplement for patients with LM.[6] In addition to RFA, TACE is also a minimally invasive treatment for LM. Vogl reported the curative effect and survival rate of 65 ovarian cancer patients with unresectable LMs treated with TACE. The median and average survival times were 14 and 18.5 months, respectively. The 1-year survival rate was 58% and the 2-year survival rate was 19%.[7] In our study, the OS times of the patients received RFA and TACE were 19.3 and 9.5 months, respectively. Compared with the resectable group, the OS of the unresectable group who received nonsurgical treatment was significantly shorter.

After conversion treatment, potentially resectable LMs are expected to be transformed into resectable lesions. It has been reported that after TACE combined with systemic chemotherapy, the response rate to metastasis can reach from 74% to 92%, and the conversion resection rate can reach from 25% to 47%.[7] In our study, there were two patients received liver section after RFA, the OS were 19 and 23 months.

Therefore, through this study and a review of the literature, we established the following treatment protocol for the patients with LMs of EOC. The patients were divided into three groups: (1) the resectable group: the metastatic tumor can be completely resected via R0 resection, and the purpose is to completely remove the tumor; (2) the potentially resectable group: the metastasis cannot be removed, but after conversion treatment (e.g., systemic chemotherapy, RFA, and TACE), R0 resection can be performed, and the purpose is to minimize the tumor and create opportunities for surgery; (3) the unresectable group: LM cannot be removed completely, the tumor may progress rapidly and have corresponding symptoms, and the purpose is to reduce the tumor as possible or at least control disease progression (Supplementary Figure 2, http://links.lww.com/CM9/A441).

In summary, for resectable LM, the OS is significantly improved after surgical resection, while nonsurgical treatment has a certain effect on LM of EOC, especially for unresectable lesions or patients, and can be used as a relatively conservative palliative treatment. Moreover, for some patients with potentially resectable metastasis, prognosis could be improved by conversion treatment and be transformed into resectable lesions.

However, there are some limitations to our study. Firstly it designed retrospectively and there may be treatment bias. Secondly, a few patients are tested for BRCA mutations, which is an important factor affecting the prognosis. Finally, the number of patients who received TACE is too small to explain the limitations of this treatment. Therefore, the established treatment protocol for LMs of EOC still needs further study.

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Conflicts of interest

None.

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