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**Review Article**

# Advances in surgical treatment of ovarian cancer liver metastasis

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## ABSTRACT

Ovarian cancer (OC) is one of the most common gynecological malignancies with characteristics of insidious onset and liver is the most common solid metastatic organ. Surgical treatment for newly diagnosed advanced or recurrent ovarian cancer liver metastasis has become a research hotspot as good outcome of patients with liver metastasis from colorectal cancer or neuroendocrine tumor by surgical treatment. It was previously considered that such patients were advanced and unfavourable for surgical treatment. However, in recent years, with the advances in liver surgical techniques, the application of three-dimensional visualization and the rise of multidisciplinary diagnosis and treatment mode, the safety of surgery has been guaranteed and the prognosis has been improved. This article reviewed the advances in surgical treatment of ovarian cancer liver metastasis.

**Keywords:** Ovarian cancer, Liver metastasis, Surgical treatment, Cytoreductive surgery, Review

## INTRODUCTION

OC is characterized by concealed onset, rapid progression, lack of effective screening methods and more than 90% of them are epithelial cancer.[1] According to the latest global cancer statistics, there were 314,000 new cases and 207,000 deaths of OC worldwide in 2020, making it the eighth most common cancer among women (incidence rate 3.4%) and the eighth leading cause of cancer death (mortality rate 4.7%).[2] In fact, more than 70% of patients with OC were initially diagnosed at advanced stage (FIGO III/IV), with poor prognosis and lost the chance of radical surgery.[3,4] The 5 year survival rate of patients with early OC was significantly different from that with advanced stage. The 5 year survival rate of FIGO stage I patients was 90%, stage II patients was about 80% and stage III/IV patients was only 30%-40% or even lower. Most patients died of tumor recurrence and drug resistance.[5,6] At present, cytoreductive surgery (CRS) combined with platinum-based chemotherapy is still the standard treatment mode for OC and implement satisfactory CRS by maximizing tumor resection is the key to the treatment of primary or recurrent metastatic OC.

Most OC patients were diagnosed as advanced stage at first visit. Liver is the most common distant solid metastatic organ (57%), followed by lung (38%), bone (4%) and brain (1%).[7] Studies have shown that more than 50% of the dead patients with OC have liver metastasis (LM) at autopsy and the more the number of metastases, the worse the prognosis.[8,9] For the patients with advanced or recurrent OC complicated with LM, it was previously considered that such patients were not suitable for surgical treatment, but in recent years, with the improvement of surgical skills, the application of three-dimensional reconstruction and the rise of multidisciplinary diagnosis and treatment mode, such metastatic lesions are no longer technical obstacles and surgical taboos. Numerous studies have shown that surgical treatment for patients with ovarian cancer liver metastasis (OCLM) is safe and effective and can improve

the prognosis of patients.[10-12] In addition, the national comprehensive cancer network (NCCN) guidelines for OC have long recommended that part of the liver, gallbladder, tail of pancreas and diaphragm can be resected as needed, in order to achieve satisfactory CRS.[13] CRS without gross residual tumor tissue (R0 CRS) is the most favorable determinant for the prognosis of OC patients and R0 hepatectomy is an important part of R0 CRS. It has been reported that every 10% R0 CRS can increase the survival rate of OC patients by 5.5%.[14]

***Pattern and clinical features***

OCLM has multiple metastasis modes including peritoneal dissemination, hematogenous metastasis and lymph node metastasis.[15] Different metastatic modes will bring different oncology characteristics, leading to different surgical plan and prognosis. Peritoneal dissemination (PD), as the most common pattern, usually leads to tumor implantation in the liver capsule, hepato-renal recess and hepatic diaphragm (right diaphragms to hepatic capsule), which might be caused by the continuous clockwise movement of OC cancer cells with intestinal peristalsis and ascites.[15,16] The incidence of PD is 40-90% and does not invade liver parenchyma, indicating OC stage III.[4,16] The incidence of diaphragmatic metastasis in advanced or recurrent OC is also very high, about 20-40%, even as high as 91%.[17,18] According to its infiltration depth, it can be divided into diaphragmatic peritoneum, subperitoneal space, diaphragmatic central tendon and pleural surface.[19] Metastases usually appear in the right diaphragm than left and once the right diaphragmatic metastasis occurs, 80% of patients will also find tumor metastases on the left side.[19] However, PD can also occur in the early stage of OC. The lesions vary in size and can be single or multiple. The main lesions are diffuse multinodular lesions including miliary and non-miliary nodules, which grow slowly and the symptoms in the liver area are often mild.[16] In some patients, small hard nodules can be palpated in the liver area. In addition, PD can directly penetrate the hepatic capsule and lead to liver parenchymal infiltration (LPI). At present, there is no clear definition of this concept and some literatures have defined it as PD with tumor invasion depth ≥2 cm in hepatic parenchyma.[10] The incidence of this type of metastasis is about 23%, which is common in elderly patients without R0 resection in the primary CRS.[16]

As a way of OCLM, the incidence of hematogenous metastasis (18%) is much lower than that of PD, but it can lead to LPM.[16] According to FIGO staging, it belongs to the latest stage of OC (IVB stage) and the prognosis is poor.[4,20] It should be noted that when the metastatic focus is located in the hepato-renal recess or hepatic diaphragm, if the tumor protrudes to the liver parenchyma, the preoperative imaging examination can be easily misdiagnosed as LPM, but intraoperative exploration confirms as PD (extrahepatic). Lymph node metastasis, as another way of OCLM can lead to liver portal lymph node metastasis (LPLNM), with the incidence of 15%, which is also an independent prognostic factor for patients with OCLM.[16,21] Preoperative CT examination can evaluate the disease, but intraoperative exploration should not be ignored.

***Diagnosis***

For newly diagnosed or recurrent OC patients, the basic diagnosis and treatment process should be followed. Specifically, the NCCN guidelines for ovarian cancer (2020 edition) can be referred to avoid missed diagnosis and misdiagnosis and accurately realize the preoperative clinical staging, physical condition evaluation and operation plan planning.[13] For the patients with liver occupying lesions in the same period, it should be identified whether the liver lesions are OC metastasis or not and should be differentiated from primary liver cancer. Patients with OCLM usually have good liver function and generally have no basic liver disease background such as hepatitis and liver cirrhosis, while the opposite is true for primary liver cancer. Therefore, routine screening of liver function, hepatitis B/C antigen and antibody should be performed; screening for alpha-fetoprotein is important. Regardless of the advanced or recurrent of OCLM, the CA125 level is significantly increased (more than 2 times of the normal value), but the alpha-fetoprotein level is within the normal range;[14] patients with advanced or recurrent of OC should be routinely evaluated with enhanced epigastric CT/MRI to assess metastasis, if necessary, with liver-specific MRI with gadoxetate disodium to determine the nature of the lesions, rather than just routine ultrasound examination to assess the upper abdomen lesions;[16,22] if necessary, PET-CT, needle biopsy and laparoscopic exploration can also be used for differentiation.

***Preoperative evaluation***

Accurate preoperative evaluation is an important measure to ensure the safety of surgery. The preoperative evaluation of OCLM can learn from the preoperative comprehensive evaluation principle of hepatectomy for liver cancer. It mainly includes the following three aspects: diagnosis, staging and determination of surgical indications. Because diagnosis and staging have been mentioned earlier, the application of three-dimensional visualization technology is emphasized here. Hepatectomy with OCLM is complex and artificial abstract stereo reconstruction based on two-dimensional image (CT/MRI) will obviously misjudge the tumor growth sites and adjacent blood vessels due to lack of experience and ability, while the three-dimensional visualization technology can intuitively and accurately display the shape and spatial distribution of liver, blood vessels, tumors and so on.[23,24] As mentioned above, LPM and implant metastases protruding to the liver parenchyma are easy to cause misdiagnosis on two-dimensional images, but such errors can be greatly reduced under three-dimensional visualization

technology. The operative indications are as follows: it can achieve postoperative residual focus ＜1 cm; only liver metastasis or extrahepatic metastasis which could be satisfactorily resected; metastatic lesion is solitary nodule or limited to one segment of the liver;[25] hepatectomy is not considered when lesions invade the left and right hepatic lobes, the hilar part of the liver and the main vena cava; patients had good general conditions, and the heart, lung, liver and kidney functions were all in the normal range; no other contraindications for hepatectomy.[25] General condition and surgical risk assessment including preoperative physical status assessment (ECOG-PS score), nutritional risk screening and nutritional status assessment (NRS2002 and PG-SGA) and vital organ function status (such as heart, lung, kidney). One study reported that patients with an ECOG-PS score of 2 to 4 are at great risk for surgery.[26] The evaluation of tumor resectability, including the evaluation and monitoring of liver function (child grade and MELD score). Child C grade or MELD score ＞11 is contraindications for hepatectomy.[27,28] In addition, evaluation of liver reserve function (indocyanine green excretion test), evaluation of basic liver disease (hepatitis virus replication, degree of liver cirrhosis), evaluation of residual liver function based on surgical planning (ratio of reserved liver volume to standard liver volume). Accurate diagnosis, individualized surgical plan and reasonable surgical approach should be made for patients with OCLM to ensure the safety of operation.

## *Treatment*

### *Surgical treatment for resectable OCLM*

First of all, it should be made clear that the surgical treatment of advanced or recurrent OCLM, whether it is partial hepatectomy, peritoneal implant resection or lymph node dissection, belongs to the category of CRS. Laparotomy may be more appropriate than laparoscopic surgery, with an oblique incision under the costal margin, an inverse 'L' incision or a median abdominal incision from the xiphoid process to the pubic symphysis.[16] Tumors arising from peritoneal metastasis can be implanted in different regions, if the tumor is only planted between the hepato-renal recess or protrudes into the hepatic parenchyma without invading the hepatic parenchyma, R0 CRS could be performed rather than hepatectomy, if there have diaphragm metastasis, according to the depth and extent of diaphragm involvement, argon beam coagulation, peritoneal resection of diaphragm surface, resection of the superficial peritoneum and muscularis involved in the diaphragm, diaphragm resection and repair are feasible.[29] If the tumor is planted on the surface of the liver capsule, wedge resection or at least 1 cm depth of the cauterization is recommended, rather than only resection of the surface lesions.[29] For LPM, the resection methods include wedge resection, local tumor resection, segmental hepatectomy and lobectomy. Wedge resection is feasible for superficial lesions, local resection of tumors is suitable for single and solitary lesions and segmental and lobectomy is suitable for lesions limited to 1-2 segments or one lobe.[30] The distance between the surgical margin and the edge of the tumor should not be less than 1 cm.[20] For liver portal lymph node metastasis as an important part of R0 CRS, 90% of the metastatic foci can be resected by R0, which can be used for hilar lymph node dissection, skeletonization and hilar lymph node dissection can be performed. However, careful operation is needed to avoid damaging the portal vessels and bile ducts.[16]

### *Treatment for unresectable OCLM*

For patients with advanced or recurrent OCLM, comprehensive treatment is essential and non-surgical treatment should be actively performed for those patients who cannot undergo surgical resection including chemotherapy (systemic and local), local ablation, transarterial chemoembolization (TACE) and targeted therapy. For those patients whose preoperative evaluation cannot achieve R0 resection or cannot tolerate surgery, although there is no specific chemotherapy for OCLM, the classical OC chemotherapy regimen of platinum combined with paclitaxel is still suitable and neoadjuvant chemotherapy (NACT) can be performed through intravenous to reduce perioperative mortality, complications and improve the possibility of RO resection.[31] In addition, hyperthermic intraperitoneal chemotherapy (HIPEC) can also be performed through local, a multicenter randomized controlled trial found that progression-free survival and overall survival were prolonged in patients with stage III ovarian cancer who underwent HIPEC after intermittent cytoreductive surgery, especially in patients with advanced ovarian cancer who relapse after initial treatment, HIPEC can significantly prolong the median survival time of patients, especially those who are sensitive to platinum.[32,33] Many prospective and retrospective studies have shown that HIPEC is feasible in the treatment of advanced and recurrent ovarian cancer. It has been reported that local ablation as a local adjuvant therapy for OCLM is feasible and effective.[34] It mainly includes radiofrequency ablation and microwave ablation, which can be percutaneous, laparoscopic or open. It is suitable for patients with OCLM such as deep lesions and a large number of tumors, which are not suitable for surgical resection. It has less effect on liver function, less trauma and can control the progression of liver metastasis to a certain extent. In addition, TACE can be used for the OCLM with poor systemic chemotherapy response and unresectable liver metastasis. As another minimally invasive palliative treatment for OCLM, the drug selection is usually mitomycin, gemcitabine and cisplatin. The 1, 2 and 3 year survival rates are 58%, 19% and 13%, respectively.[35] It can reduce the tumor size to a certain extent and prolong the survival time. Finally, targeted therapy has brought great changes to the treatment of OC, which has attracted the attention of doctors and patients due to its small side effects and

strong specificity. As the first antiangiogenic targeted drug in clinical application, bevacizumab is valuable in first-line treatment, platinum-sensitive recurrence and platinum-resistant recurrence of ovarian cancer. Its combination with chemotherapy can prolong the progression-free survival time by 3.8 months.[36] In addition, PARP inhibitors (oxalapril, nilapril) significantly delayed the time of recurrence and prolonged the progression-free survival, especially for patients with BRCA gene mutation/HRD positive.[37,38] As a new maintenance therapy, PARP inhibitors change the treatment mode of OC into the whole-process management mode of surgery+chemotherapy+targeted maintenance therapy.

## CONCLUSION

Surgical treatment is safe and effective for patients with advanced or recurrent OCLM. For patients with clear surgical indications, surgery can effectively improve the prognosis of patients; for patients who cannot undergo surgery, comprehensive treatment including chemotherapy, targeted therapy, liver ablation and TACE should be actively given. Besides, in the MDT era, the treatment of such patients requires multi-disciplinary cooperation. Liver surgeons and gynecologist should work together to develop individualized treatment plans, achieve accurate surgery and improve the treatment mode of ovarian cancer.

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