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LIVER METASTASIS IN ADVANCED OVARIAN CANCER AFTER CHEMOTHERAPY: A CASE REPORT

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Abstract

Ovarian cancer is the most lethal disease among gynecologic malignancies; about 1/4 of ovarian cancer patients are in stage IV when diagnosed. Based on the data of Globocan, there were 295,414 newly diagnosed ovarian cancer patients and 184,799 deaths registered in 2018. For ovarian epithelial cancer patients with stage IV disease, the mean overall survival (OS) is around 20 months, and the 5 year-OS is about 20%. About 1 in 5 patients with advanced-stage ovarian cancer have hepatobiliary involvement. The study on HGSOC aims to understand the molecular and genetic features, diagnosis, and prognosis of HGSOC, as well as its response to therapy. The method involves analyzing the genetic traits, chromosomal instability, and dysregulation of signaling pathways associated with HGSOC, as well as the detection of stemness and EMT levels in response to chemotherapy and radiation therapy. The results highlight the unique characteristics of HGSOC, such as nearly universal mutation in and dysfunction of p53, genomic instability, and the role of cancer stem cells and EMT in chemo- and radiation resistance. The implication of the study is the need for a better understanding of the molecular basis of HGSOC for improved diagnosis, prognosis, and treatment strategies.

Keyword: Ovarian cancer, liver metastase, chemotherapy

Introduction

Ovarian cancer is the most lethal disease among gynecologic malignancies; about 1/4 of ovarian cancer patients are in stage IV when diagnosed (Bray et al., 2018; Shan et al., 2022). Ovarian cancer is a prevalent and deadly malignant cancer in females that is often diagnosed at an advanced stage with extensive metastasis (Siegel et al., 2021). Based on the data of Globocan, there were 295,414 newly diagnosed ovarian cancer patients and 184,799 deaths registered in 2018 (COPD, n.d.; Mendes et al., 2019). A previous study has reported that in the United States, there was about 21,750 newly diagnosed ovarian cancer patients and 13,940 deaths caused by ovarian cancer in 2020 (Siegel et al., 2021).

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A study found that about 490,142 deaths due to ovarian was reported among 19,296,319,576 person-years at risk for women in China from 1990 to 2019 (Z. Wang et al., 2021). Ovarian cancer is often silently spilled and patients were mainly diagnosed as an advanced disease, which becomes one of the most lethal gynecological malignancy (Z. Wang et al., 2021). Approximately 70% of ovarian cancer patients were diagnosed with synchronous distant metastases due to the limited early, specific symptoms and effective screening strategies (Stewart et al., 2019).

Two types of liver lesions occur in ovarian cancer patients: liver parenchymal metastasis (LPM) and liver parenchymal invasion (LPI). LPI develops from perihepatic or diaphragmatic peritoneal metastasis (M. Wang et al., 2019). It is important for gynecologic oncologists to distinguish between LPM and LPI. LPM is classified as his stage IVB and is a type of hematogenous metastasis with short survival, whereas LPI is a type of peritoneal transplant disease that does not adversely affect prognosis. The definition of LPI is currently unknown. This was defined as a diaphragmatic or perihepatic peritoneal implant with liver involvement of at least 2 cm, irregular or absent interface between the lesion and the liver, and replacing part of the liver parenchyma (O'Neill et al., 2017). Patients with LPI should be treated the in the same way as those with LPM. For LPI lesions less than 4 cm in diameter, wedge resections without distinguishing the segmental anatomy are often used for preservation of liver volume (Shan et al., 2022).

Liver was identified to be the most common distant metastatic organ of ovarian cancer in stage IV which accounted for 37%–57%, followed by distant lymph nodes, lung, bone and brain (Deng et al., 2018; Gardner et al., 2020). Metastasis is the leading cause of death in ovarian cancer patients, with only 29% of women diagnosed with metastatic ovarian cancer having a 5-year survival rate. Despite continued improvements in chemotherapy drugs and advances in surgical techniques, the 5-year survival rate was only 29%. Survival rate is only 29%. Annual Survival Rates for Ovarian Cancer Patients Still Less Than 50% (Cai & Liu, 2021). The 2-year recurrence free survival of ovarian cancer patients was about 48%, less than 50% (Benoit et al., 2022). To identify factors associated with the mortality of patients with metastatic ovarian cancer is essential for improving the prognosis of these patients. Moreover, the study on HGSOC aims to understand the molecular and genetic features, diagnosis, and prognosis of HGSOC, as well as its response to therapy.

Research Methods

The patient (Mrs. E) was a P2L2, 47-year-old referral from an oncology polyclinic with recidive ovarian carcinoma + susp hepar metastase. Previously the patient complained of abdominal pain since 3 months ago. There is no history of an enlarged abdomen, no bleeding from the vagina, no fever, drastic weight loss in the last 2 months (+). The patient has not menstruated in the last 4 years. The patient had 2 children

The patient was previously known with ovarian carcinoma and was treated with debulking. From the results of the PA examination, the results of PA were obtained: High grade serous carcinoma of the ovary metastasizing to the omentum, rectum, ileum, sigmoid, right and left paracolic, subhepatic and prevesical. The first operation was in 2019 on General Hospital in Bukittinggi, then the patient was treated with chemotherapy.

Then in April 2021, the patient went to Dr. M. Djamil General Central Hospital Padang with complaints of an enlarged stomach. At the time of examination suspected of a metastasis to the liver. Then the patient was operated on again by joining the digestive

section and the tissue was examined at the PA laboratory. The results of metastatic carcinoma to the liver were obtained. The patient was then treated with chemotherapy again. In October 2022, the patient returned with complaints of nausea and vomiting and abdominal pain. The patient was re-examined and examined by CT scan.

Based on physical examination, the patient appears to be moderately ill, BP: 120/80 mmHg, pulse 84 x / min, breathing 22 x / min, temperature 36.7 ^{o}C, body high 155 cm, weight 54 kg, BMI 22.5 kg / m2, on abdominal examination in the abdominal was not enlarged, there was tenderness, dull percussion and bowel sounds (+) normal. Gynecological examination was found the uterus of the vaginal vulva is quiet without any vaginal bleeding. From CT scan it was found residive left ovarian tumor with intrahepatic and splenic metastases, peritoneal carcinomatosis of the left upper abdomen.

Because the patient has had 2 operations and has finished chemotherapy, the patient is given the option of whether he still wants to have surgery by removing part of the liver tissue which might worsen the patient's condition or simply continue with further chemotherapy. The patient chooses to undergo surgery with all the risks. Then the patient was operated on again in collaboration with the digestive department for hepatectomy.

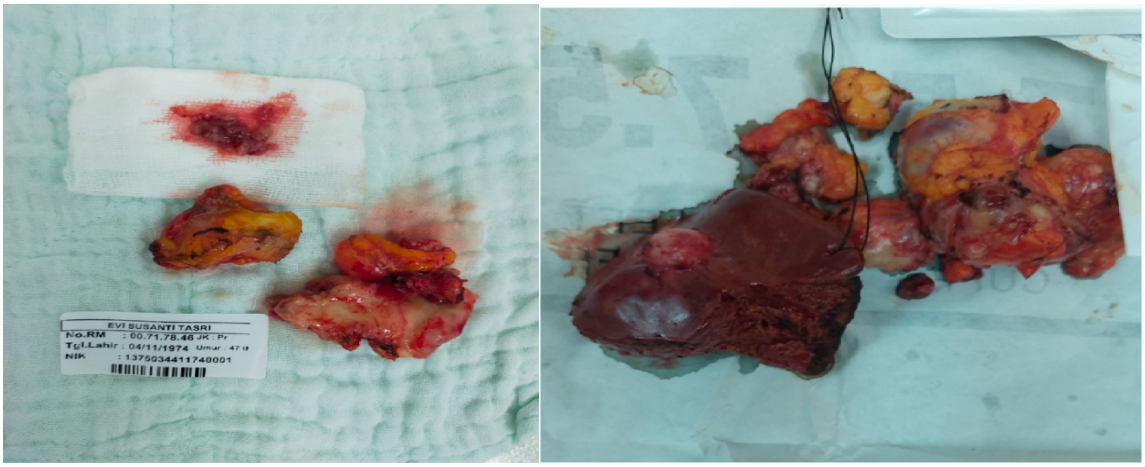
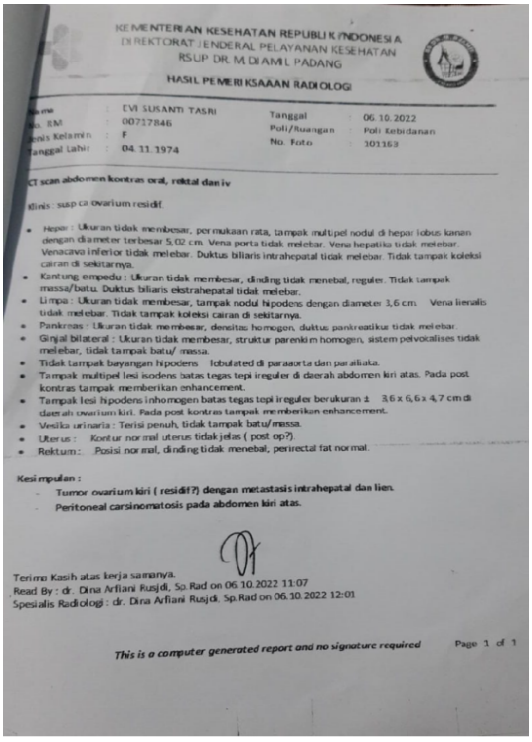


Figure 1. Tissue in the third debulking laparotomy

Figure 2. CT Scan examination



KEMENTERIAN KESEHATAN REPUBLIK INDONESIA
DIREKTORAT JENDERAL PELAYANAN KESEHATAN
RSUP DR. M. DJAMIL PADANG

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Tanggal Lahir : 04.11.1974
Tanggal : 06.10.2022
Poli/Ruangan : Poli Kebidanan
No. Foto : 101163

CT scan abdomen kontras oral, rektal dan iv

Klinis : susp ca ovarium residif

- Hepar : Ukuran tidak membesar, permukaan rata, tampak multipel nodul di hepar lobus kanan dengan diameter terbesar 5,02 cm. Vena porta tidak melebar. Vena hepatika tidak melebar. Venacava inferior tidak melebar. Duktus biliaris intrahepatal tidak melebar. Tidak tampak koleksi cairan di sekitarnya.
- Kantung empedu : Ukuran tidak membesar, dinding tidak menebal, regular. Tidak tampak massa/batu. Duktus biliaris ekstrahepatal tidak melebar.
- Limpa : Ukuran tidak membesar, tampak nodul hipodens dengan diameter 3,6 cm. Vena lienalis tidak melebar. Tidak tampak koleksi cairan di sekitarnya.
- Pankreas : Ukuran tidak membesar, densitas homogen, duktus pankreatikus tidak melebar.
- Ginjal bilateral : Ukuran tidak membesar, struktur parenkim homogen, sistem pelvocalises tidak melebar, tidak tampak batu/ massa.
- Tidak tampak bayangan hipodens lobulated di paraaorta dan paraliliata.
- Tampak multipel lesi isodens batas tegas tepi ireguler di daerah abdomen kiri atas. Pada post kontras tampak memberikan enhancement.
- Tampak lesi hipodens inhomogen batas tegas tepi ireguler berukuran ± 3,6 x 6,6 x 4,7 cm di daerah ovarium kiri. Pada post kontras tampak memberikan enhancement.
- Vesika urinaria : Terisi penuh, tidak tampak batu/massa.
- Uterus : Kontur normal uterus tidak jelas (post op?)
- Rektum : Posisi normal, dinding tidak menebal, perirectal fat normal.

Kesimpulan :
- Tumor ovarium kiri (residif?) dengan metastasis intrahepatal dan lien.
- Peritoneal carsinomatosis pada abdomen kiri atas.

Terima Kasih atas kerja samanya.
Read By : dr. Dina Arfiani Rusjdi, Sp.Rad on 06.10.2022 11:07
Spesialis Radiologi : dr. Dina Arfiani Rusjdi, Sp.Rad on 06.10.2022 12:01

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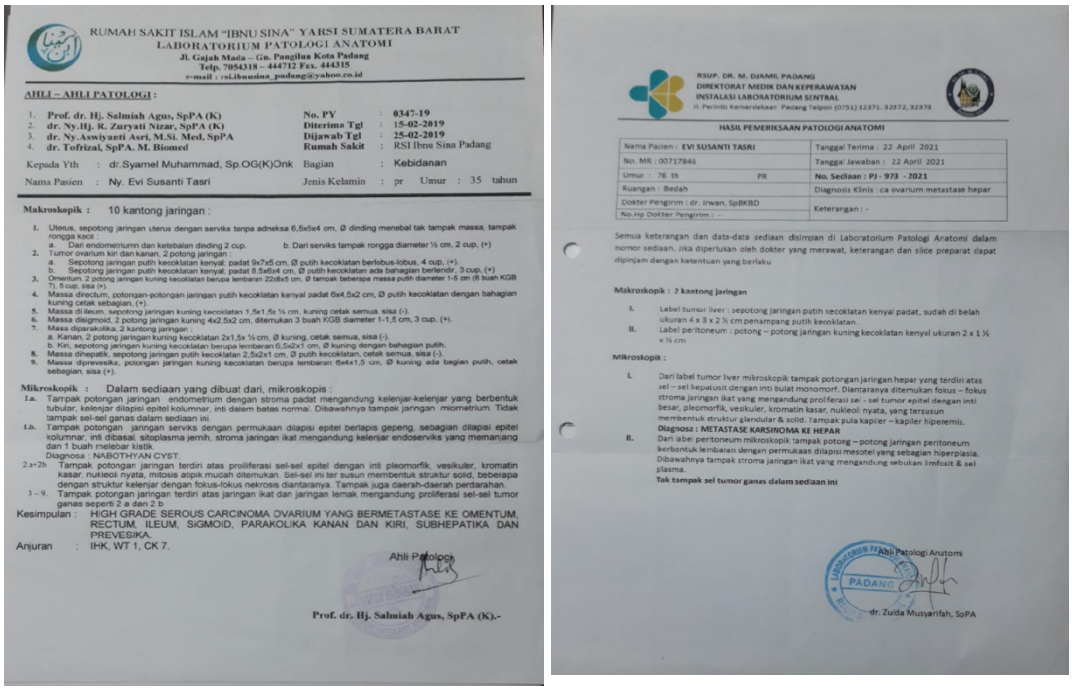
Page 1 of 1

Figure 3. CT Scan result



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Nama Pasien : Ny. Evi Susanti Tasri
Jenis Kelamin : pr Umur : 35 tahun

Makroskopik : 10 kantong jaringan :

1. Uterus, sepotong jaringan uterus dengan serviks tanpa adneksa 6,5x5x4 cm, Ø dinding menebal tak tampak massa, tampak rongga kecil.
   a. Dari endometrium dan ketebalan dinding 2 cup. b. Dari serviks tampak rongga diameter ½ cm, 2 cup, (+)
2. Tumor ovarium kiri dan kanan, 2 potong jaringan :
   a. Sepotong jaringan putih kecoklatan kenyal, padat 9x7x5 cm, Ø putih kecoklatan berlobus-lobus, 4 cup, (+).
   b. Sepotong jaringan putih kecoklatan kenyal, padat 8,5x6x4 cm, Ø putih kecoklatan ada bahagian berlendir, 3 cup, (+)
3. Omentum, 2 potong jaringan kuning kecoklatan berupa lembaran 22x8x5 cm, Ø tampak beberapa massa putih diameter 1-5 cm (6 buah KGB ?), 5 cup, sisa (+).
4. Massa directum, potongan-potongan jaringan putih kecoklatan kenyal padat 6x4,5x2 cm, Ø putih kecoklatan dengan bahagian kuning cetak sebagian, (+).
5. Massa di ileum, sepotong jaringan kuning kecoklatan 1,5x1,5x ¼ cm, kuning cetak semua, sisa (-).
6. Massa disigmoid, 2 potong jaringan kuning 4x2,5x2 cm, ditemukan 3 buah KGB diameter 1-1,5 cm, 3 cup, (+).
7. Massa diparakolika, 2 kantong jaringan :
   a. Kanan, 2 potong jaringan kuning kecoklatan 2x1,5x ½ cm, Ø kuning, cetak semua, sisa (-).
   b. Kiri, sepotong jaringan kuning kecoklatan berupa lembaran 6,5x2x1 cm, Ø kuning dengan bahagian putih.
8. Massa dihepatik, sepotong jaringan putih kecoklatan 2,5x2x1 cm, Ø putih kecoklatan, cetak semua, sisa (-).
9. Massa diprevesika, potongan jaringan kuning kecoklatan berupa lembaran 6x4x1,5 cm, Ø kuning ada bagian putih, cetak sebagian, sisa (+).

Mikroskopik : Dalam sediaan yang dibuat dari, mikroskopis :

1a. Tampak potongan jaringan endometrium dengan stroma padat mengandung kelenjar-kelenjar yang berbentuk tubular, kelenjar dilapisi epitel kolumnar, inti dalam batas normal. Dibawahnya tampak jaringan miometrium. Tidak tampak sel-sel ganas dalam sediaan ini.
1b. Tampak potongan jaringan serviks dengan permukaan dilapisi epitel berlapis gepeng, sebagian dilapisi epitel kolumnar, inti dibasal, sitoplasma jernih, stroma jaringan ikat mengandung kelenjar endoserviks yang memanjang dan 1 buah melebar kistik.
Diagnosa : NABOTHYAN CYST.
2.+2h. Tampak potongan jaringan terdiri atas proliferasi sel-sel epitel dengan inti pleomorfik, vesikuler, kromatin kasar, nukleoli nyata, mitosis aitpik mucah ditemukan. Sel-sel ini ter susun membentuk struktur solid, beberapa dengan struktur kelenjar dengan fokus-lokus nekrosis diantaranya. Tampak juga daerah-daerah perdarahan.
3 – 9. Tampak potongan jaringan terdiri atas jaringan ikat dan jaringan lemak mengandung proliferasi sel-sel tumor ganas seperti 2 a dan 2 b.

Kesimpulan : HIGH GRADE SEROUS CARCINOMA OVARIUM YANG BERMETASTASE KE OMENTUM, RECTUM, ILEUM, SIGMOID, PARAKOLIKA KANAN DAN KIRI, SUBHEPATIKA DAN PREVESIKA.
Anjuran : IHK, WT 1, CK 7.

Ahli Patologi
Prof. dr. Hj. Salmiah Agus, SpPA (K).-

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Umur : 76 th PR	No. Sediaan : PJ - 973 - 2021
Ruangan : Bedah	Diagnosis Klinis : ca ovarium metastase hepar
Dokter Pengirim : dr. Irwan, SpBKBD	Keterangan : -
No.Hp Dokter Pengirim : -	

Semua keterangan dan data-data sediaan disimpan di Laboratorium Patologi Anatomi dalam nomor sediaan. Jika diperlukan oleh dokter yang merawat, keterangan dan slice preparat dapat dipinjam dengan ketentuan yang berlaku

Makroskopik : 2 kantong jaringan

I. Label tumor liver : sepotong jaringan putih kecoklatan kenyal padat, sudah di belah ukuran 4 x 3 x 2 ½ cm penampang putih kecoklatan.
II. Label peritoneum : potong – potong jaringan kuning kecoklatan kenyal ukuran 2 x 1 ½ x ½ cm

Mikroskopik :

I. Dari label tumor liver mikroskopik tampak potongan jaringan hepar yang terdiri atas sel – sel hepatosit dengan inti bulat monomorf. Diantaranya ditemukan fokus – fokus stroma jaringan ikat yang mengandung proliferasi sel - sel tumor epitel dengan inti besar, pleomorfik, vesikuler, kromatin kasar, nukleoli nyata, yang tersusun membentuk struktur glandular & solid. Tampak pula kapiler – kapiler hiperemis.
Diagnosa : METASTASE KARSINOMA KE HEPAR
II. Dari label pertoneum mikroskopik tampak potong – potong jaringan peritoneum berbentuk lembaran dengan permukaan dilapisi mesotel yang sebagian hiperplasia. Dibawahnya tampak stroma jaringan ikat yang mengandung sebukan limfosit & sel plasma.
Tak tampak sel tumor ganas dalam sediaan ini

Ahli Patologi Anatomi
dr. Zulda Musyarifah, SpPA

Figure 4. Phatological Results shows high grade serous carcinoma ovarium metastases to the omentum, rectum ileum, sigmoid, right and left paracolics, subhepatics, and prevesica

Results and Discussion

Ovarian cancer is the most lethal disease among gynecologic malignancies; about 1/4 of ovarian cancer patients are in stage IV when diagnosed (Bray et al., 2018; Shan et

al., 2022). Ovarian cancer is a prevalent and deadly malignant cancer in females that is often diagnosed at an advanced stage with extensive metastasis (Siegel et al., 2021). Based on the data of Globocan, there were 295,414 newly diagnosed ovarian cancer patients and 184,799 deaths registered in 2018 (COPD, n.d.).

High-grade serous ovarian carcinoma (HGSOC) represents the most common form of epithelial ovarian carcinoma (Siegel et al., 2018). The absence of specific symptoms leads to late-stage diagnosis, making HGSOC one of the gynecological cancers with the worst prognosis. The cellular origin of HGSOC and the role of reproductive hormones, genetic traits (such as alterations in P53 and DNA-repair mechanisms), chromosomal instability, or dysregulation of crucial signaling pathways have been considered when evaluating prognosis and response to therapy in HGSOC patients. However, the detection of HGSOC is still based on traditional methods such as carbohydrate antigen 125 (CA125) detection and ultrasound, and the combined use of these methods has yet to support significant reductions in overall mortality rates (Punzón-Jiménez et al., 2022).

Two types of liver lesions occur in ovarian cancer patients: liver parenchymal metastasis (LPM) and liver parenchymal invasion (LPI). LPI develops from perihepatic or diaphragmatic peritoneal metastasis. It is important for gynecologic oncologists to distinguish between LPM and LPI. LPM is classified as his stage IVB and is a type of hematogenous metastasis with short survival, whereas LPI is a type of peritoneal transplant disease that does not adversely affect prognosis. The definition of LPI is currently unknown. This was defined as a diaphragmatic or perihepatic peritoneal implant with liver involvement of at least 2 cm, irregular or absent interface between the lesion and the liver, and replacing part of the liver parenchyma (O'Neill et al., 2017). Patients with LPI should be treated the in the same way as those with LPM. For LPI lesions less than 4 cm in diameter, wedge resections without distinguishing the segmental anatomy are often used for preservation of liver volume (Shan et al., 2022).

For tumors requiring the resection of one liver segment, nonmajor anatomic resection will minimize blood loss and allow a safe excision. In ovarian cancer, segmentectomy of 5 or 6 segments is more commonly needed. Patients may benefit from this more conservative approach because of the preservation of liver volume. To achieve a safe resection, techniques include the use of portal triad clamping selectively, keeping low intravascular volumes during parenchymal transection, hemostasis, and biliostasis with caution. A hepatobiliary surgeon is recommended for this procedure. Considering the goal of optimal cytoreduction for ovarian cancer, there are still controversies regarding whether a resection margin greater than 1 cm is needed, especially in patients with LPI. In recent years, minimally invasive laparoscopic LR has also benefited patients with liver involvement. The most common complication of surgery is pleural effusions, and other rare complications include bleeding, liver abscess, and bile or pancreatic leakage (Shan et al., 2022).

Liver was identified to be the most common distant metastatic organ of ovarian cancer in stage IV which accounted for 37%–57%, followed by distant lymph nodes, lung, bone and brain (Deng et al., 2018; Gardner et al., 2020). Metastasis is the leading cause of death in ovarian cancer patients, with only 29% of women diagnosed with metastatic ovarian cancer having a 5-year survival rate. Despite continued improvements in chemotherapy drugs and advances in surgical techniques, the 5-year survival rate was only 29%. Survival rate is only 29%. Annual Survival Rates for Ovarian Cancer Patients Still Less Than 50% (Cai & Liu, 2021). The 2-year recurrence free survival of ovarian cancer patients was about 48%, less than 50% (Benoit et al., 2022). To identify factors

associated with the mortality of patients with metastatic ovarian cancer is essential for improving the prognosis of these patients.

Liver resection is the best choice for ovarian cancer patients with liver involvement. Other conservative treatments, such as thermal ablation techniques, TACE, and CT-HDRBT, are recommended for patients who are not eligible for surgery.

Difficulties in the early detection of HGSOC, before the disease develops to advanced stages, can be attributed to the lack of specific symptoms, which are usually missed or attributed to other pathologies (Punzón-Jiménez et al., 2022). In clinical practice, the diagnosis of EOC is based on four main techniques: pelvic palpation examination (PPE), imaging (which includes transvaginal ultrasound or sonography, magnetic resonance imaging, computed tomography, and positron-emission computed tomography), serum levels of specific proteins, and surgery (either laparoscopic or laparotomic) (Punzón-Jiménez et al., 2022).

Ranked as one of the most aggressive and deadly forms of gynecological cancer, HGSOC is currently considered to be a public healthcare issue that significantly impacts female patients' quality of life. Current challenges arise from the difficulty in establishing an early and effective diagnosis in patients with adnexal masses. HGSOC is mostly diagnosed in advanced FIGO stages (III-IV) due to the lack of symptoms and the use of traditional diagnostic methods. The performance of CA125—the only available molecular serum biomarker—alone or in combination with other biomarkers or TVS, has yet to support significant reductions in mortality rates (Punzón-Jiménez et al., 2022).

Other strategies have focused on the possible dual origin of HGSOC (the FTE or OSE) and the influence of hormones in promoting or protecting against the development of disease. Furthermore, HGSOC is characterized by extensive genomic instability, promoted by almost universal mutations in the TP53 gene, genes belonging to the HRR system, and CIN. Furthermore, alterations in multiple signaling pathways and epigenomic mechanisms have also been described (Punzón-Jiménez et al., 2022).

Research in this field is rapidly moving forward, allowing the molecular management of HGSOC by encompassing multiple disease-associated features in high-throughput, personalized approaches. Proof of such advances includes the putative gene panels and expression analyses intended for the stratification of HGSOC, the establishment of treatment-guided decisions, and the monitoring of disease progression, which can be extended to early detection (Punzón-Jiménez et al., 2022).

Conclusion

Liver was identified to be the most common distant metastatic organ of ovarian cancer in stage IV which accounted for 37%–57%, followed by distant lymph nodes, lung, bone and brain. Metastases is a major cause of mortality in ovarian cancer patients, and the 5-year survival rate was only 29% among women diagnosed with distant-metastatic ovarian cancer.

Liver resection is the best choice for ovarian cancer patients with liver involvement. Other conservative treatments, such as thermal ablation techniques, TACE, and CT-HDRBT, are recommended for patients who are not eligible for surgery.

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