

World Journal of *Hepatology*

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The primary aim of *World Journal of Hepatology (WJH, World J Hepatol)* is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJH* as 0.61. The *WJH*'s CiteScore for 2020 is 5.6 and Scopus CiteScore rank 2020: Hepatology is 24/62.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Editorial Office Director: *Xiang Li*.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pylsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

September 27, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Addressing hepatic metastases in ovarian cancer: Recent advances in treatment algorithms and the need for a multidisciplinary approach

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Author contributions: Halkia E initially conceived of and designed the study and provided coordination and supervision throughout the project; Adamopoulou K and Gkamprana AM performed the literature review, data collection and prioritization, and drafted the manuscript; Halkia E and Patsouras K revised the manuscript for scientific content; Spelling and grammatical corrections were made by Halkia E; Adamopoulou K and Gkamprana AM contributed equally and share first authorship; All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors report that they have no conflicting interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

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Abstract

The lifetime risk for ovarian cancer incidence is 1.39% and the lifetime risk of death is 1.04%. Most ovarian cancer patients are diagnosed at advanced stages (III, IV) because there were no specific symptoms or existing screening tests. Liver metastases have been found in up to 50% of patients dying of advanced ovarian cancer. Recent studies indicate the need for a multidisciplinary approach from initial diagnosis to oncologic surgery and chemotherapy treatment, mandating the involvement of gynecologic oncologists, surgical oncologist, medical oncologists, hepatobiliary surgeons, and interventional radiologists.

Key Words: Cancer; Metastases; Ovarian; Hepatic; Multidisciplinary

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Core Tip: Each year more than 295000 women are diagnosed with and 185000 die from ovarian cancer, which remains the most lethal of all gynecologic malignancies worldwide. The management of advanced ovarian cancer has evolved over the past two decades. Surgical excision and with different minimally invasive techniques are available options for treating hepatic metastasis. A multidisciplinary approach is essential to achieve optimal treatment outcomes.

Citation: Adamopoulou K, Gkamprana AM, Patsouras K, Halkia E. Addressing hepatic metastases in ovarian cancer: Recent advances in treatment algorithms and the need for a multidisciplinary approach. *World J Hepatol* 2021; 13(9): 1122-1131

URL: <https://www.wjgnet.com/1948-5182/full/v13/i9/1122.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v13.i9.1122>

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 8, 2021

Peer-review started: April 8, 2021

First decision: July 8, 2021

Revised: July 21, 2021

Accepted: August 11, 2021

Article in press: August 11, 2021

Published online: September 27, 2021

P-Reviewer: Li CG, Plagens-Rotman K

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Li X



INTRODUCTION

Each year more than 295000 women are diagnosed with and 185000 die from ovarian cancer, which remains the most lethal of all gynecologic malignancies, worldwide[1, 2]. There is currently no screening test for ovarian cancer and early symptoms are usually misleading and scarce, resulting in an advanced stage at diagnosis. As a result, about two-thirds of cases are diagnosed at a late metastatic stage, and 12%-33% are International Federation of Gynecology and Obstetrics (FIGO) stage IV[3]. Ovarian cancer metastatic patterns include peritoneal and lymph node dissemination as well as hematogenous spread[4]. Peritoneal dissemination is the most common pattern of spread in FIGO stage III ovarian cancer, usually in a form of miliary tumor foci, with possible involvement of the hepatic capsule and right hemidiaphragm. According to the FIGO classification, perihepatic metastases are considered as stage III, while liver parenchymal metastases are stage IV[5]. Up to 50% of women dying of some sort of gynecologic cancer had concurrent liver metastatic disease at autopsy[6,7]. Staging, optimal cytoreductive surgery, and platinum-based chemotherapy are historically considered the standard of care for newly diagnosed advanced stage ovarian cancer. However, up to 90% of women who were optimally debulked and had adjuvant chemotherapy eventually relapse with disease progression[8]. An alternative treatment for initially inoperable disease consists of neoadjuvant chemotherapy followed by cytoreduction[9,10]. The strongest predictor of disease progression in any case is the level of cytoreduction, even in the interval setting, and it usually determines overall survival[11-13]. Complete cytoreduction is important, and exceptional surgical skill is required to achieve "no visual tumor" throughout the abdominal cavity, especially in difficult-to-treat areas, such as the upper abdomen during the operation. Complete cytoreduction may require procedures, such as peritonectomy, diaphragmatic resection, and multiple visceral resections[14-19]. Liver metastases of ovarian cancer are considered for surgical therapy, but with controversial indications and patient selection criteria. Addressing liver metastases of ovarian cancer origin still represents a barrier to complete cytoreduction. Several studies have reported the feasibility and efficacy of hepatic resection in the setting of advanced ovarian cancer [20-22]. There are several other treatment modalities of liver metastases, such as thermal radiofrequency (RFA) or microwave (MWA) ablation, cryoablation, laser induced thermotherapy (LITT), transarterial chemoembolization (TACE), computed tomography-guided high dose-rate brachytherapy (CT-HDRBT) and stereotactic body radiation therapy (SBRT). In this review, we aim to summarize recent advances in the management of ovarian cancer liver metastases. The value of the involvement of different medical and surgical specialties and subspecialties is discussed. A multidisciplinary approach to advanced ovarian cancer is essential to achieve optimal treatment outcomes.

METHODOLOGY

A review of literature on the management of liver metastases of ovarian cancer was performed. A comprehensive search of the National Library of Medicine MEDLINE/PubMed database was performed for articles published in the last two decades. The date of the last search was February 28, 2021. The search strategy included the keywords "ovarian," "cancer," "hepatic," "liver," "metastasis, -es," and "multidisciplinary." Articles relevant to the subject in the citations of each report were additionally included. Articles that were written in non-Latin alphabets were excluded for translational reasons.

SURGICAL PROCEDURES

Radical surgical resection plus postoperative treatment of liver metastases of colorectal origin have gradually evolved as a standard of care in many cancer centers, with reports of 5-year overall survival of such patients reaching 50% or more[23,24]. Results of recent studies treating patients with liver metastases of neuroendocrine origin, report a 5-year overall survival exceeding 65%[25]. Generally, recent data show a better prognosis with liver metastases originating from the genital system than with those from other non-colorectal, non-neuroendocrine primaries[26,27]. Recent trends of treatment of advanced ovarian cancer are based on the application of cytoreductive surgery; hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and radical

excision of all intraperitoneal disease, including the upper abdomen, with a curative intent and a clear survival benefit[28-30]. About 40% of women diagnosed with advanced stage ovarian cancer present with a concurrent bulky tumor load in the upper abdomen (*i.e.* the diaphragm, stomach, or liver), requiring cytoreductive surgery[31].

Liver mobilization, hepatic capsular metastases resection, liver segmentectomy, and diaphragmatectomy are surgical treatment procedures described by Wang *et al*[32]. Specifically, they recommend wedge excision or at least 1 cm of ablation depth for hepatic capsular metastases, rather than superficial excision. Diaphragmatic resection and repair rather than diaphragmatic peritoneal dissection should be applied for metastatic tumors located between the right hemidiaphragm and liver capsule. In case an anatomical resection is performed, a resection margin of more than 2 cm is required. If the metastatic disease involves porta hepatis, hepatic portal skeletonization, portal lymph node dissection should be performed.

In a study by Kamel *et al*[33] in 2011, a significant survival benefit was demonstrated for patients with ovarian cancer liver metastases treated with surgical resection *vs* patients with a similar tumor burden who had biopsy only. Median overall survival from the time of the diagnosis of liver metastatic disease was 53 mo *vs* 21 mo. Similar results were reported by a multicenter study of 2655 patients with ovarian cancer liver metastases who underwent cytoreduction in the upper abdomen[29]. The median overall survival was 54.6 mo for patients who were completely debulked. The importance of complete cytoreduction (R0) not only in the lower abdomen, but also with liver involvement was discussed by Bristow *et al*[34]. They reported an overall survival of 50.1 mo for patients who had undergone R0 Liver resection and R0 cytoreduction, *vs* a 20-mo overall survival of patients treated with an R0 cytoreduction and a non-R0 liver resection. Bolton and Fuhrman[35] conducted a study on a group of patients who had fewer than three liver metastases and another group having more than four lesions at the time of liver resection. Surprisingly, the investigators reported no difference in survival when complete excision of the hepatic tumors was achieved.

Several studies have reported on the safety and efficacy of upper abdominal cytoreductive including diaphragmatic and hepatobiliary resection[22,31,36-38], but others have reported major complications linked with that kind of surgical treatment[39]. Chi *et al*[36] reported the most common postoperative complications in a group of 141 patients treated with upper abdominal cytoreduction of liver metastases. They included pancreatic leaks, intraperitoneal ascitic fluid accumulation, and symptomatic pleural effusions. The reported overall morbidity and mortality were 22% and 1.4% respectively. A review by Gasparri *et al*[22] included studies in which liver resection was performed at either the time of primary treatment or the time of recurrence. The investigators reported no complications attributed to liver resection in the first category and only minimal complications in the second, including bilioma and transient liver function test abnormalities. The most important prognostic factors were the extent of residual disease and patient performance status. Similar perioperative outcomes and rates of complications were reported in cases of cytoreduction including either both upper and lower abdomen or solely the lower abdomen[22,40]. A major survival benefit may be safely achieved with surgical removal of liver tumor deposits during primary, secondary, tertiary and even quaternary cytoreduction[22,31]. According to Neuman *et al*[41], tumor dissemination pattern, cancer antigen (CA)-125 value, age, and initial stage of disease or level of resectability of the tumor did not seem to affect outcome. However, the presence of ascites and the location of tumor aggregates in both liver lobes are associated with a worse prognosis.

THERMAL ABLATION TECHNIQUES

Thermal ablation techniques in liver surgery include RFA, MWA, cryoablation, and LITT. Locoregional ablation is effectively applied in patients with liver metastases considered inoperable because of surgical or anesthetic contraindications. In cases where liver lesions are parenchymal and not localized on the surface or Glisson's capsule, percutaneous local ablation is feasible and effective without the use of anesthesia. Such patients recover treatment sooner and are fit to receive adjuvant chemotherapy. Usually, hepatic metastases of ovarian cancer origin are superficial, and can only be ablated intraoperatively to protect surrounding tissues from thermal injury. Contraindications to such locoregional ablative intraoperative treatment include tumor location near the hepatic hilum, porta hepatis, or near large bile ducts. Compared with surgical removal of tumors, local ablation is usually associated with a

higher rate of recurrence, while lesions greater than 3 cm are usually not satisfactorily ablated[22]. Another obvious limitation of thermal ablation procedures compared with surgical resection is the lack of a surgical margin, as simple post ablation radiographic findings are used to determine efficacy. Only highly selected patients undergo such treatment procedures, and the local control and long-term survival benefits are still pending from large multicenter prospective studies.

RFA

RFA is a minimally invasive procedure in which high frequency alternating current is delivered through an electrode directly to the tumor, providing ablation and eventually cell death while sparing surrounding tissues from unnecessary damage. Low morbidity and mortality are attributed to this minimally invasive technique with a therapeutic intent. Many studies report a morbidity rate from 2%-5.7% and a mortality rate of less than 1% associate with RFA treatment. Patient safety is clearly greater with RFA than with liver resection, which has a reported treatment-associated morbidity of 25% and mortality of less than 5%[42-44]. RFA is indicated in selected patients with ovarian cancer liver metastases, numerous metastases, large metastases, or with foci located deep within the liver parenchyma[45-47]. Effective local tumor control has been reported in several studies of RFA in liver metastases, with a limited number of reported complications, such as bleeding, liver abscess, and rare cases of bile leakage. In 2014, Liu *et al*[47] reported no serious complications after the application of RFA in ovarian cancer liver metastases, with 1-, 3-, and 5-year overall survival rates of 100%, 61%, and 61% respectively. In 2005, Mateo *et al*[48] reported the outcomes achieved with RFA combined with excisional surgery for hepatic metastases. Prospective randomized controlled studies are eagerly awaited in order to get a better idea of the therapeutic benefit provided by the application of either RFA and/or liver resection in the treatment of hepatic metastases originating from ovarian cancer.

MWA

MWA is a minimally invasive method of thermal ablation. It uses electromagnetic energy in the microwave spectrum to increase intratumoral temperature and achieve large ablation volume[49,50]. Zhuo *et al*[51] reported that MWA (50 w × 10 min) achieved acceptable perioperative morbidity and mortality and reduced blood loss, transfusion volume, and cost compared with surgical resection of metastatic lesions. However, patients treated with MWA had a significantly higher mortality in terms of overall survival.

LITT

LITT uses neodymium-doped yttrium aluminum garnet laser light to induce therapeutic coagulation. This laser technique uses thin flexible fibers and a water-cooled applicator. A sphere of necrosis is produced from a bare fiber, while a diffuser fiber accomplishes ablation in an elliptical shape. In the multi-applicator mode, a single lesion can be ablated with the simultaneous use of up to five laser applicators [52].

Cryoablation

This ablation technique induces cell death in a target lesion by alternate freezing and thawing[53]. Gao *et al*[54] investigated the efficacy and safety of cryoablation in the treatment of ovarian cancer hepatic metastases. The post ablation local tumor progression rate was 7.14%, and the 1-year overall survival was over 90%. No serious complications (*e.g.*, liver bleeding, cryo-shock, hepatic failure, abscess, biliary fistula, renal insufficiency or others) were reported. A constellation of post ablation symptoms was observed in about half the patients, including low grade fever and malaise, and abdominal pain and was described as "postcryoablation syndrome". Elevated transaminases and right-side pleural effusion were noted in a few patients. Goering *et al*[55] found similar relapse-free rates in patients treated with cryoablation combined with hepatic resection surgery and those with surgery alone. They suggested that cryoablation could increase the number of patients eligible to surgery.

TACE

TACE has been historically used to treat primary and metastatic liver tumors. It consists of local arterial infusion of chemotherapy drugs plus embolization particles [50]. TACE is recommended for the treatment of hepatocellular cancer and liver

metastases, especially those originating from colorectal or neuroendocrine malignancies[24,56-61]. Ovarian cancer patients usually undergo cytoreductive surgery and may then receive adjuvant treatment by chemoembolization of secondary liver lesions. TACE indications for the treatment of hepatic metastases include tumors that do not respond to chemotherapy, unresectable tumors, or toxicity of chemotherapeutic agents. Generally, it is used as a last attempt to control intrahepatic metastases while preserving good liver function[62].

SBRT

SBRT, also known as stereotactic ablative radiotherapy (SABR) is a form of external beam radiotherapy that delivers a high dose of radiation in a single or a few fractions, with accuracy sufficient to hit a target and at the same time minimize the induced injury to surrounding tissues[63]. In the phase II SABR-COMET trial[64], 99 patients with hepatic oligometastases of one to five lesions from a variety of primary tumors including breast, colorectal, lung, and prostate were included. They were randomized to two groups based on whether they had received SBRT or standard palliative treatment. The authors reported a higher median overall survival in the SBRT group, 41 mo *vs* 28 mo. Toxicities greater than grade 2 were reported more often in the SBRT group (29% *vs* 9%). Three treatment related deaths (4.5%) were reported. Because of the paucity of randomized studies, the efficacy of SBRT in ovarian cancer remains elusive.

Yegya-Raman *et al*[65] conducted a systematic review of the role of SBRT in the treatment of oligometastatic gynecologic malignancies, primarily ovarian cancer. Seven of eight studies reported response rates > 75%, and 14 of 16 reported local tumor control rates of > 80%. No toxicities greater than grade 3 were documented in 56% of the studies. In ten studies, the median progression-free survival was between 3.3 and 9.7 mo. Disease progression was usually observed outside the SBRT field. The efficacy of SBRT for management of liver metastases was similar to that of RFA, as indicated by the reported 2-year overall survival[66]. Systemic therapy is usually combined with SBRT, as it has been observed that the therapeutic combination addresses the tendency for distant progression, with less toxicity. Kunos *et al*[67] reported on the almost concurrent use of SBRT and systemic chemotherapy. The grade 3-4 toxicities that were documented were mainly hematologic and metabolic and were most likely chemotherapy related. Another combination therapy includes SBRT plus immunotherapy and has had positive results. In conclusion, the use of SBRT should be seriously considered as an alternative to surgery or chemotherapy, especially in patients with low performance status, already overtreated, or not suited for more aggressive procedures.

COMPUTED TOMOGRAPHY-GUIDED HIGH DOSE-RATE BRACHYTHERAPY

In 2004, Ricke *et al*[68,69] described the use of computed tomography-guided high dose-rate brachytherapy (CT-HDRBT) in clinical practice. CT-HDRBT is a locally applied radioablation technique administers iridium-192 through catheters into the tumor for a short time under CT guidance. The technique does not require cooling of adjacent large vessels, and tumor size is not a burden. CT-HDRBT is recommended as an effective and feasible way to treat unresectable primary and secondary hepatic tumors. It has excellent local tumor control, time to disease progression, and overall survival outcomes[70,71]. A small study by Colletini *et al*[72] investigated the efficacy and safety of HDRBT in the treatment of ovarian cancer hepatic oligometastases. They reported that the method was safe and had an excellent local control rate. The overall 12-mo survival rate for a 12-mo period was 100%. CT-HDRBT can be effectively used to treat advanced ovarian cancer synchronous and metachronous liver metastases as a combined therapeutic approach with primary cytoreductive surgery or interval debulking.

MULTIDISCIPLINARY APPROACH

Building a multidisciplinary team (MDT) is essential for the optimal treatment of patients with advanced ovarian cancer and liver metastases. National Comprehensive Cancer Network guideline algorithms of ovarian cancer management recommend the involvement of gynecologic oncologists, pathologists if a biopsy is available, radiologists, interventional radiologists, anesthesiologists, hepatobiliary surgeons, and physicians certified to perform cytoreductive surgery[73]. All cancers should be discussed at MDT committee meetings, which time the treatment algorithms are chosen. The presence of an anesthesiologist is recommended in order to discuss the eligibility for surgery of each patient[74]. A Cochrane Review found that centralization of ovarian cancer surgical oncology services improved overall survival[75]. Management of patients by MDTs is more likely to lead to correct staging[76], evidence-based management, appropriate, and well-timed treatment[77]. As for the surgical subspecialties, intraoperative collaboration of gynecologic oncologists with colorectal and hepatobiliary surgeons is more likely to achieve a complete cytoreduction[78]. As radiographic findings, especially CT, are essential for preoperative evaluation as well as postoperative follow-up, participation of competent radiologists is valuable in patient management and decision making[79]. Interventional radiologists use a variety of techniques to perform the above mentioned minimally invasive procedures. It is clear that the involvement of different disciplines improves the quality of care and shows professionalism in gynecological cytoreductive surgery.

CONCLUSION

The management of advanced ovarian cancer has evolved over the past decade. Parenchymal hepatic metastases are no longer considered as an exclusion criterion when deciding whether a patient is eligible for optimal debulking. Various surgical and minimally invasive procedures with acceptable local control and toxicity profiles, represent valid options for treating liver metastases. Further investigation, ideally by randomized controlled trials, is needed to identify the subset of patients that will most likely benefit from each therapeutic modality. Building a MDT is of outmost importance when treating ovarian cancer liver metastases and will enhance therapeutic outcomes.

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