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REVIEW – CLINICAL ONCOLOGY

Hepatic resection during cytoreductive surgery for primary or recurrent epithelial ovarian cancer

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Abstract
Purpose Surgical cytoreduction remains a cornerstone in the management of patients with advanced and recurrent epithelial ovarian cancer. Parenchymal liver metastases determine stage VI disease and are commonly considered a major limit in the achievement of an optimal cytoreduction. The purpose of this manuscript was to discuss the rationale of liver resection and the morbidity related to this procedure in advanced and recurrent ovarian cancer.
Methods A search of the National Library of Medicine's MEDLINE/PubMed database until March 2015 was performed using the keywords: "ovarian cancer," "hepatic," "liver," and "metastases."
Results In patients with liver metastases, hepatic resection is associated with a similar prognosis as stage IIIC patients. The length of the disease-free interval between primary diagnosis and occurrence of liver metastases, as well as residual disease after resection, is the most important prognostic factors. In addition, the number of liver lesions, resection margins, and the gynecologic oncology group performance status seem to play also an important role in determining outcome.
Conclusions In properly selected patients, liver resections at the time of cytoreduction increase rates of optimal cytoreduction and improve survival in advanced-stage and recurrent ovarian cancer patients.

Keywords Cytoreduction · Debulking surgery · Liver metastases · Hepatectomy · Ovarian cancer · Recurrent ovarian cancer

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Introduction

In the USA, approximately 22,000 women are diagnosed with epithelial ovarian carcinoma (EOC) every year (Siegel et al. 2012). Unfortunately, the majority of the patients are diagnosed at an advanced stage (Cannistra 2004). Under these circumstances, the extirpation of all visible disease is the surgical goal; a systematic meta-analysis has shown that with every 10 % of increased optimal cytoreduction, there is a 5.5 % increase in survival (Bristow et al. 2002; Du Bois et al. 2009). Neoadjuvant chemotherapy followed by interval debulking is an alternative to primary cytoreduction in patients with advanced, large-volume disease or poor performance status (Vergote et al. 2010; Kehoe et al. 2015). However, even in this setting, at the time of interval debulking surgery, residual disease is the strongest independent variable predicting overall survival. The achievement of an optimal cytoreduction also allows for adjuvant intraperitoneal chemotherapy, which has been associated with a survival advantage over standard intravenous chemotherapy and with the longest overall survival reported so far in EOC (Armstrong et al. 2006).

Similarly, in case of recurrence the recurrent setting, an optimal cytoreduction with the extirpation of all visible disease seems to be critical in determining the survival benefit (Chi et al. 2006; Harter et al. 2006; Zang et al. 2011). Based on these data, the surgical treatment of advanced-stage EOC has evolved, extending to the upper abdomen and becoming multivisceral. In cancer centers, surgeries such as bowel resection, peritonectomy, diaphragmatic resection, splenectomy, partial pancreatectomy, and cholecystectomy are considered to be an integral part of the surgical EOC treatment (Meredith et al. 2003; Eisenkop et al. 2006; Magtibay et al. 2006; Aletti et al. 2006; Papadia and Morotti 2013; Chi et al. 2009). However, disease to the liver still represents a limit to a complete surgical treatment.

Only a few small studies have evaluated the benefit of hepatic resection in patients with various gynecological malignant tumors (Eisenhauer et al. 2006; Alseidi et al. 2006; Chalkiadakis et al. 2005; Tangjitgamol et al. 2004; Peterhans et al. 2011). Furthermore, no valid predictive factors for optimal surgical outcome after hepatic resection have yet been identified. The aim of this manuscript is to review the indication for hepatic resection in ovarian cancer patients and discuss its clinical outcome and morbidity.

Materials and methods

We have performed a review of the English literature on liver resections in the context of cytoreduction of EOC and related conditions. A comprehensive search of the National Library of Medicine's MEDLINE/PubMed database was performed for articles published from inception to March 2015. The following keywords were used: "ovarian cancer," "hepatic," "liver," and "metastases." Case reports and research published only in abstract format were not included. Studies were considered if they were original reports on the outcome of hepatic surgery in patients with primary or recurrent EOC. Articles relevant to the subject in the citations of each report were additionally included.

Literature data and discussion

Liver metastasectomy in non-EOC surgery

Improvement in surgical techniques, along with the use of new technologies such as navigated liver resection, better perioperative management, and a better understanding of segmental liver anatomy, has led in the recent past to an increase in hepatic resections for metastatic disease. Metastatic colorectal cancer represents the most common indication for hepatic metastasectomy. In series from this setting, current operative mortality and 5-year survival rate are 5 and 40 %, respectively (Kanas et al. 2012; Veereman et al. 2015; Adam et al. 2006). For non-colorectal and non-neuroendocrine liver metastases, the role of liver resections is less well defined. Liver metastases usually occur via hematogenous spread and are considered evidence of "systemic disease" with an elevated risk of concomitant extrahepatic disease (Lee 1984). Hence, traditionally, these patients have not been considered for salvage surgery and have been treated with systemic chemotherapy (Adam et al. 2006). However, a recent multicenter study showed that liver resection for non-colorectal, non-neuroendocrine metastases is becoming more common (Adam et al. 2006). Interestingly, in a large retrospective series on patients undergoing hepatic resections for metachronous liver metastases from non-colorectal and non-neuroendocrine cancers, patients with reproductive tract primary cancers had better disease-free and overall survival as compared to patients with non-reproductive tract primary cancers (Weitz et al. 2005). Similarly, case reports suggest that in selected gynecologic oncology patients the excision of liver metastases may provide a long-term complete remission, alleviating the need for systemic chemotherapy and a survival advantage (Papadia et al. 2011).

Liver metastasectomy in EOC

Up to 15 % of the patients with EOC will be diagnosed with FIGO stage IV disease, for example the presence of parenchymal liver metastases and/or distant metastases beyond the pelvis (Prat 2015). Hepatic parenchymal metastases account for 18 % and were the second most common cause of stage IV disease in a large GOG study (Winter et al. 2008). Additionally, liver metastases are found in up to 50 % of patients dying of EOC (Rose et al. 1989). Given the importance of a radical surgical approach both at initial diagnosis and in the case of recurrence, hepatic resections may come into question in a significant number of patients.

In ovarian cancer, perihepatic metastases occur by means of peritoneal spread of tumor implants on the liver surface. At times, a perihepatic metastasis can invade the liver parenchyma. Hepatic metastases via hematogenous spread do occur as well. Different ways of metastatic spread to the liver may represent diseases with different inherent biological characteristics and may therefore carry a different prognosis. Particularly in ovarian cancer, where at least part of liver parenchymal metastases occur by the same means as other abdominal implants and where residual disease after cytoreductive surgery is one of the most important and the only prognostic factor that can be influenced by the physician, the matter of hepatic resections is of utmost importance.

Liver resection at the time of primary disease

To answer the question of whether patients with advanced-stage ovarian cancer benefit from liver resection, a prospective randomized trial should be performed. However, given ethical considerations, the years needed to accrue a significant number of patients, and the complexity of the surgery involved, such a trial will most likely not be conducted. Indirect evidence for the benefit of hepatic resections could be obtained by retrospective comparison of outcomes from patients with stage IIIC and stage IV ovarian cancer because of parenchymal liver metastases subjected to complete cytoreduction. If the hypothesis that parenchymal liver metastases in ovarian cancer occur via transcoelomic implantation of tumor cells that grow in the liver parenchyma and have therefore similar biological behavior as the other abdominal implants, patients with stage IIIC and stage IV ovarian cancer with comparable bulk of initial disease, submitted to optimal cytoreductive surgery, should have similar oncologic outcomes regardless of liver involvement. Other evidence may derive from series comparing stage IV ovarian cancer patients in whom liver resections were performed with those who were not subjected to hepatic resections. However, these comparisons may be flawed by selection bias, as patients in whom liver resections are successfully performed may represent a cohort of patients with less initial tumor burden, better performance status, and other good prognostic factors.

So far, the available evidence on this topic is limited. In a retrospective review of 360 stage IV EOC patients enrolled in GOG studies who underwent surgical cytoreductive surgery followed by six cycles of intravenous platinum/paclitaxel chemotherapy at multivariate regression analysis histology, malignant pleural effusions, intraparenchymal liver metastases, and residual tumor size were significant prognostic variables (Winter et al. 2008).

In 1999, Bristow et al. (1999) first reported a survival advantage in stage IV EOC patients with liver parenchymal metastases who underwent an optimal cytoreductive surgery which included liver resections. Median survival of 50.1, 27.0, and 7.6 months was recorded in 6 patients undergoing optimal cytoreduction of hepatic and extrahepatic disease, in 11 patients undergoing optimal cytoreduction of extrahepatic disease with residual hepatic lesions, and in 20 patients with suboptimal hepatic and extrahepatic cytoreduction, respectively. In their cohort of 84 patients with stage IV EOC, optimal cytoreduction and performance status were associated with improved survival at multivariate analysis. Thirty-two percentage of the patients of the entire cohort experienced postoperative complications with a mortality rate of 6 %. The most common complications were wound infections and pneumonia. No complications that were related specifically to liver surgery, such as biliary leak or liver abscesses, were reported. The causes of postoperative deaths were not reported.

In 2005, Loizzi et al. (2005) reported on 29 patients with primary and recurrent epithelial ovarian cancer with liver involvement. Median age was 59 years. Median disease-free interval for patients presenting with recurrent disease was 29 months. Optimal cytoreduction, defined as residual disease <1 cm, was achieved in 62 % of the patients. Surgical details on the type of surgical resection and complication rates were not reported. Median overall survival after liver surgery with liver resection was 19 months for patients with primary, 24 and 10 months for patients undergoing secondary and tertiary cytoreduction, respectively. At univariate analysis, histology, performance status at the time of primary tumor diagnosis, number of hepatic lesions, the presence of extrahepatic disease, and treatment with platinum-based chemotherapy correlated with survival.

In 2009, Lim et al. (2009) reported on 16 patients with primary stage IV EOC at their institution. In two patients (12.5 % of the cases), the metastases were located deeply in the parenchyma and were deemed unresectable. In the other 14 patients (87.5 % of the cases), the metastases were superficial (with depth of parenchymal invasion of <1 cm) and were removed. Median age of the patients was 54 years. Wedge resection, segmentectomy, and hemihepatectomy were performed in 50, 36, and 14 % of the cases, respectively. Resection margins were negative in every case. The patients who underwent successful hepatic resections were compared with 97 stage IIIC patients treated at the same institution in the same time interval. Among the two groups, median age at diagnosis, histology, tumor grade, median CA 125, and percentage of patients undergoing neoadjuvant chemotherapy were similar. Similar surgical procedures were performed on patients in the two groups, aside from cholecystectomies, which were more frequent in patients with stage IV disease. Similar optimal cytoreduction rates were achieved in the two groups: 94 and 93 %, respectively, for stage IIIC and stage IV patients. Surgical morbidity was similar for the two groups. No biliary leak or liver abscesses were reported. Median progression-free survival was 23 and 26 months for stage IIIC and stage IV patients, respectively. Five-year overall survival rates were 55 and 51 % for stage IIIC and stage IV patients, respectively. They recommend that stage IV patients with liver metastatses be divided into two groups: those with liver involvement secondary to hematogenous spread and to transcoelomic seeding. The first group is characterized by a bleak prognosis and should be treated with systemic chemotherapy; the second group has a similar prognosis as stage IIIC patients and should be submitted to surgery with hepatic resections.

In 2012, Neumann et al. (2012) reported on 70 patients with primary and recurrent EOC and liver metastases. Liver disease was considered unresectable in 41 % of the cases, whereas 58.6 % of the patients underwent some form of liver resection. Additional surgical procedures were similar among patients undergoing liver surgery and those who did

Table 1 Intra- and postoperative data on cytoreductive surgery with liver resections for primary ovarian cancer

References	Number of pts	Median age (years)	Optimal cytoreduction rate	Type of liver surgery	EBL (ml)	OR time (min)	LOH (days)	Complications (%)
Bristow et al. (1999)	37/84[a]	61 (26–85)	6/37 (16 %)[c]	NA	726 (50–4000)	188 (60–340)	13.8 (4–48)	Pneumonia (5 %) Wound complications (14 %) Small bowel obstruction (8 %) Large bowel obstruction (4 %) Deep venous thrombosis (6 %) Pulmonary embolus (4 %) Myocardial infarction (2 %) Postoperative death (6 %)
Lim et al. (2009)	16/113[b]	54 (36–77)	13/14 (93 %)[d]	Wedge resection 50 % Segmentectomy 35.7 % Hemi-hepatectomy 14.3 %	1500 (500–2000)	577 (295–687)	19 (6–60)	Fever (14.3 %) Pancreatic leak (14.3 %) Pleural effusion (14.3 %)

EBL estimated blood loss, *OR time* operating room time, *LOH* length of hospital stay

[a] Number of patients undergoing liver surgery/number of patients with stage IV disease

[b] Number of patients with liver metastases/number of patients enrolled (stage IIIC and stage IV)

[c] Only patients with liver metastases

[d] Only patients with parenchymal liver metastases from peritoneal seeding

Table 2 Oncologic outcome of cytoreductive surgery with liver resections for primary ovarian cancer

References	Number of pts	Median age	5-year PFS	Optimal liver metastases resection rate in pts with liver metastases	Negative liver resection margins	OS (months)
Bristow et al. (1999)	37/84[a]	61 (25–85)	NA	16 %	NA	Overall: 18.1 Optimally cytoreduced pts: 38.4 Suboptimally cytoreduced pts: 10.3
Lim et al. (2009)	16/113[b]	54 (36–77)	25 % stage IIIC 23 % stage IV	100 %[c]	100 %[c]	55 % 5-year OS for stage IIIC pts 51 % 5-year OS for stage IV pts

NA data not available

[a] Number of patients with liver metastases/number of patients with stage IV disease

[b] Number of patients with liver metastases/number of patients enrolled (stage IIIC and stage IV)

[c] Only patients with parenchymal liver metastases from peritoneal seeding

Table 3 Prognostic factors in patients undergoing cytoreductive surgery with liver resections for primary ovarian cancer

References	Number of patients	Univariate analysis	Multivariate analysis
Bristow et al. (1999)	37/84[a]	Residual disease < or >1 cm ($p = 0.0004$)[b] GOG PS ($p = 0.0026$)[b] Number of salvage chemotherapy regimens ($p = 0.0039$)[b] Optimal debulking of extrahepatic disease ($p = 0.0001$) Optimal debulking of extrahepatic and hepatic disease ($p = 0.0001$) Number of liver lesions <3 ($p = 0.0012$)	Residual disease GOG PS Number of salvage chemotherapy regimens
Lim et al. (2009)	16/113[c]	NA	NA

GOG PS GOG performance status, *NA* data not available

[a] Number of patients undergoing liver surgery/number of patients with stage IV disease

[b] Referred to all the samples (not only hepatic metastatic ovarian cancer patients)

[c] Number of patients with liver metastases/number of patients enrolled (stage IIIC and stage IV)

not, with the exception of small bowel resections, which were more frequent among patients not undergoing liver surgery. Surgical morbidity was similar in the two groups. Again, no complications that are specifically related to liver surgery, such as biliary leak or liver abscesses, were reported. The 3-month mortality rate was significantly higher in the group of patients with non-resectable liver disease. Median survival was 42 months for patients undergoing liver resection with negative margins and 4, 6, and 5 months for patients undergoing R1, R2 resections, and for patients not undergoing liver resections, respectively. The presence of preoperative ascites and bilobular liver involvement were associated with a poorer overall survival at multivariate analysis. The authors recommend an extensive cytoreduction with liver resections if a R0 resection can be achieved.

In summary, in these series, no complications specifically related to the liver resections have been reported and perioperative data are roughly similar to the data from cytoreductive surgery without liver resections (Table 1). Oncologic outcome seems to be improved in patients in whom a complete resection of the liver lesions can be achieved (Table 2). Residual disease and performance status seem to be the most important prognostic factors (Table 3).

Liver resection at the time of recurrence disease

Although secondary cytoreduction at the time of recurrent disease is more controversial than surgery at primary diagnosis, the greatest amount of literature on hepatic resections in EOC has been produced in this setting. This is not surprising, since secondary cytoreduction is usually performed when the bulk of abdominal disease is relatively small and confined. Additionally, recurrent EOC patients who are subjected to surgery are usually selected on the basis of performance status and the relatively mild biological behavior of their disease. Still, the current literature consists only of retrospective series with limited number of patients.

In 2003, Meredith et al. (2003) reported on 26 patients with recurrent ovarian cancer to the liver subjected to secondary cytoreductive surgery with complete segmentectomies or more extensive hepatic surgery in over two decades at Mayo Clinic. The hepatic resections were performed by hepatobiliary surgeons. Hepatic lesions were multiple in 9 cases and single in 17. At the time of hepatic resection. 20 patients underwent additional surgical procedures. In 18 patients, residual disease was absent at the end of the surgery, and in 3 and 5 patients residual disease was ≤1 and >1 cm, respectively. Postoperatively, four patients required transfusion of more than 4 units of packed red blood cells (PRBCs), one developed a superficial wound infection, and one required a reoperation secondary to a small bowel perforation. Median survival was significantly higher for patients optimally cytoreduced (27.3 vs. 8.6 months) and for patients with a disease-free interval >12 months before secondary cytoreduction (27.3 vs. 5.7 months). Interestingly, the number of liver lesions and bilobar involvement did not affect outcome. The authors conclude that the presence of parenchymal liver metastases should not preclude attempts of secondary optimal cytoreduction.

In 2003, Yoon et al. (2003) reported on 24 patients with recurrent ovarian or fallopian tube carcinoma located to the liver. Median size of the largest liver lesion was 5 cm. Lesions were multiple in 7 cases, uni and bilobar localization were 23 cases and 1 case, respectively. Trisegmentectomies, lobectomies, segmentectomies, and wedge resections were performed in 2, 2, 17, and 3 cases, respectively. Complications occurred in 21 % of the cases, with two patients presenting hepatic surgery-related complications (biloma). Resection margins were negative in 13 patients. Optimal cytoreduction to no residual disease and to <1 cm was achieved in 22 and 3 patients, respectively. The median overall survival was 62 months. No significant prognostic factors for overall survival were identified at univariate analysis. The authors recommend that liver resections for recurrent fallopian tube and ovarian cancer be performed in patients with favorable tumor biology and good performance status.

In 2010, Pekmezci et al. (2010) reported on eight patients with recurrent ovarian cancer with isolated liver metastases who underwent hepatic resections. Median progression-free survival prior to hepatic resection was 5.4 years. Wedge resections, segmentectomies, left lateral sectorectomy, and right hepatectomy were performed in 2, 3, 2, and 1 cases, respectively. Additional procedures, such as locoregional lymphadenectomy and intra-abdominal tumor implant excision, were performed in three cases. Median largest tumor diameter was 4.5 cm. Optimal cytoreduction to no residual disease was achieved in every case. Median progression-free survival after hepatic resection was 39 months. The authors conclude that liver resections in carefully selected patients are feasible and effective.

In 2010, Abood et al. (2008) reported on ten patients undergoing liver resections for recurrent ovarian cancer. Of note is that two of these patients were not of epithelial origin (one granulosa cell tumor and one yolk sac tumor). Median disease-free interval before liver surgery was 48 months. Liver resections consisted in trisegmentectomy, lobectomy, and bisegmentectomy in four patients, five patients, and one patient, respectively. Although none of the patients showed extrahepatic disease on radiologic imaging at work-up, nine presented with localized extension of their disease and required additional surgical procedures to achieve optimal cytoreduction, including diaphragmatic resections, bowel resections, and adrenalectomy in 6, 3, and 1 cases, respectively. Median tumor diameter was 4.7 cm, average number of hepatic lesions was 4, and pathologic negative resection margins were achieved in 5 patients. Prognostic factors correlating with improved survival were largest liver lesion ≥5 cm and negative margin status. Median overall survival after liver resections was 33 months. The recommendation of the authors is to consider all patients with isolated liver metastases from ovarian cancer for surgical resection.

In 2011, Roh et al. (2011) reported on 18 patients with recurrent ovarian cancer with liver lesions who underwent hepatic surgery at the time of secondary cytoreduction. Hepatic resections comprised non-anatomical wedge resection in 22.2 %, anatomical unisegmentectomy in 72.2 %, or bisegmentectomy in 5.6 % of the cases and were performed by hepatobiliary surgeons. Median diameter of the largest liver lesion was 4.5 cm. Liver lesions were unilobar in 83.3 % of the cases and bilobar in 16.7 % of the cases. Negative hepatic resection margins were achieved in 66.7 % of the cases. Additional cytoreductive procedures to debulk extrahepatic disease were performed in 72.2 % of the cases. Optimal cytoreduction, defined as ≤1 cm residual disease, was achieved in 66.7 % of the cases. Median estimated blood loss was 340 ml, median hospital stay was 15.5 days, and only one major complication (large bowel perforation) was recorded. Five minor complications, including wound infection and dehiscence, small bowel ileus, bile leak, transient abnormality in liver function test, and pleural effusions, were managed conservatively. Median overall survival after hepatic resection was 38 months. At univariate analysis, prognostic factors predicting a better outcome were greater disease distribution in the pelvis than in the abdomen, optimal cytoreduction, and negative liver resection margins. Outcome of these patients was compared with that of 25 patients with unresectable liver disease that underwent secondary cytoreductive surgery without liver resections over the same period. Both groups had similar age, histology, grade, and primary cytoreductive outcome at presentation. Patients not undergoing liver resections had greater abdominal disease distribution, bilobar involvement, suboptimal secondary cytoreduction rates, and significantly worse outcome with a median overall survival of 10 months. The authors conclude that hepatic resection for recurrent ovarian cancer is safe and should not be considered a contraindication to a secondary cytoreduction. Given the impact of an optimal cytoreduction and of negative liver resection margins on survival, hepatic resections should be performed only when these goals are thought to be achievable.

In 2012, Niu et al. (2012) reported on 60 patients with recurrent ovarian cancer to the liver undergoing secondary cytoreduction with liver resection. Disease-free interval was ≥12 months in 65 % of the cases. Liver lesions were single and multiple in 40 and 60 % of the cases, respectively. Liver lesions were unilateral and bilateral in 48.3 and 51.7 % of the cases, respectively. The median number of treated lesions was 3. Liver resections were performed via wedge resection in 46.7 %, radiofrequency ablation (RFA) in 5 %, lobectomy in 11.7 %, trisegmentectomy in 11.7 %, bisegementectomy in 20 %, and combined RFA in 5 % of the cases, respectively. Hepatic resections achieved microscopic negative margins in 90 % of the cases. Ten percentage of the patients experienced postoperative complications, none of which were related to liver resections. Median overall survival was 39 months. Median overall survival decreased from 52 months in patients with microscopically negative liver resection margins to 22 months in positive liver resection margins. At univariate analysis, disease-free interval >12 months, single liver lesion, and negative resection margins were associated with improved survival. At multivariate analysis, only negative resection margins maintained statistical significance. The presence of extrahepatic disease was not a negative prognostic factor. The authors suggest that hepatic resections be performed in case of recurrent ovarian cancer provided that the resection margins are negative.

In 2014, Kolev et al. (2014) reported on 27 patients undergoing liver surgery for recurrent EOC with parenchymal liver metastases. Median age at the time of liver resection was 62 years. Median disease-free interval before liver resection was 27 months. Hepatic lesions were single and multiple in 44 and 56 % of the cases, respectively. Median tumor size was 4.5 cm. Lesions were located in one or both lobes of the liver in 22 and 5 cases, respectively. Liver resections consisted in multisegmentectomy, lobectomy, segmentectomy, and wedge resections in 3, 4, 11, and 9 cases, respectively. Resection margins were negative in 24 patients. In nine patients, additional surgical procedures, such as diaphragmatic resection, large bowel resection, and splenectomy, were performed. Cytoreduction to no visible disease or to <1 cm was achieved in 25 patients. Median estimated blood loss was 300 ml, median length of surgery was 209 min, and median length of hospital stay was 6 days. Overall, 11 % of the patients developed postoperative complications, with one ICU admission following sepsis and two reoperations following anastomotic bowel leak. Median overall survival after liver resection was 12 months. Factors associated with improved survival were a progression-free interval of >24 months and optimal cytoreduction. The number of liver lesions was not a prognostic factor. The authors recommend considering liver resections at the time of secondary cytoreduction, as this seems to improve outcome.

In summary, in these series, only a relatively small percentage of patients experienced complications specifically related to the liver resections, such as bilioma or transient abnormality in liver function tests (Table 4). Oncologic outcome seems to be improved in patients in whom a complete resection of the disease can be achieved (Table 4). Disease-free interval and residual disease are the most important prognostic factors (Table 5). The number of liver lesions, the resection margins, and the GOG performance status seem to play an important role in determining outcome as well.

Surgical technique

Generally, all approaches begin with a midline xifo-pubic incision with the patient in reverse Trendelenburg position. This incision is usually sufficient to provide adequate exposure for liver mobilization and wedge resections. A right subcostal incision also provides excellent exposure and is the preferred access if only hepatic metastases or metastases in the upper quadrant are present.

Self-retaining retractor systems should be used, as these are essential to safely dissect out major veins and to fully visualize the diaphragm, suprahepatic inferior vena cava, and liver veins. In all explorations, in order to determine the extent of disease in patients with known upper abdominal disease, we mobilize the right hepatic lobe. We begin such mobilization by identifying the infrahepatic inferior vena cava and the suprahepatic inferior vena cava. The liver is attached anteriorly to the abdominal wall by the round and falciform ligaments. The peritoneal surface of the falciform ligament turns into the right and left coronary ligaments, which reflect off the liver capsule on the diaphragm. The anterior coronary ligaments run on the posterior liver edge, where they join the posterior right and left coronary ligaments to form the right and left triangular ligaments. The coronary ligaments on each side delineate the bare areas of the liver, which underlie the central tendon of the

Table 4 Surgical and oncologic outcome on cytoreductive surgery with liver resections for recurrent ovarian cancer

References	Number of pts	Median age (years)	Optimal cytoreduction rate	Type of liver surgery	Negative resection margins	Complications (%)	OS (months)
Meredith et al. (2003)	26	62	80.8 %	Segmentectomy 69.2 % Trisegmentectomies 3 % Left hepatectomy 3.8 % Right hepatectomy 15.4 %	NA	Transfusion of more than 4 uPRBC (15.4 %) Superficial wound infection (3.8 %) Small bowel perforation that Requiring reoperation (3.8 %)	Overall: 26.3 Optimally cytoreduced: 27.3 Suboptimally cytoreduced: 8.6 ($p = 0.031$)
Yoon et al. (2003)	24	53	66.7 %	Wedge resection 12.5 % Segmentectomy 70.9 % Trisegmentectomy 8.3 % Lobectomy 8.3 %	54.1 %	Biloma (8.3 %) Prolonged ileus, urinary tract infection, and pneumonia (4.2 %)	62 (95 % CI 41–83)
Loizzi et al. (2005)[a]	29	54	NA	NA	NA	NA	Hepatic disease only: 25 (9–44) Multiorgan recurrence: 8 ($p = 0.033$) Single hepatic lesion: 25 (3–44) Multiple liver lesions: 10 (3–23) ($p = 0.038$)[a]
Abood et al. (2008)	10	51	100 %	Bisegmentectomy 10 % Trisegmentectomy 40 % Lobectomy 50 %	50 %	Anemia (10 %)	33 (95 % CI 19–56)
Pekmezci et al. (2010)	8	56.1	NA	Wedge resection 25 % Segmentectomy 37.5 % Sectorectomy 37.5 %		NA	24
Roh et al. (2011)	18	52.5	66.7 %	Wedge resection 22.2 % Segmentectomy 72.2 % Bisegmentectomy 5.6 %	66.7 %	Transverse colon perforation (5.6 %) Wound infection and dehiscence (5.6 %) Small bowel ileus (5.6 %) Bile leakage (5.6 %) Transient liver function test abnormality (5.6 %) Pleural effusion (5.6 %)	38 (3–78)

Table 4 continued

References	Number of pts	Median age (years)	Optimal cytoreduction rate	Type of liver surgery	Negative resection margins	Complications (%)	OS (months)
Niu et al. (2012)	60	46	NA	Wedge resection (46.7 %) Bisegmentectomy (20.0 %) Trisegmentectomy (11.7 %) Lobectomy (11.7 %) Radiofrequency ablation (5 %) Combined radiofrequency ablation (5 %)	90 %	Wound infection and pulmonary complications (10 %)	39 (5–79)
Neumann et al. (2012)[a]	70	59	NA	NA	NA	Sepsis (2.4 %) Infection (7.3 %) Anastomotic leak (4.9 %) Bleeding (4.9 %) Multiorgan failure (7.3 %) 30-Day mortality (7.3 %)	Optimally cytoreduced: 42 Suboptimally cytoreduced: 4.6 ($p < 0.001$)
Kolev et al. (2014)	27	62	92.6 %	Wedge resection (33.3 %) Segmentectomy (40.7 %) Multisegmentectomy (11.1 %) Lobectomy (14.8 %)	88.9 %	Anastomotic leak (7.4 %) Sepsis (3.7 %)	56 (12–249)

NA data not available, *uPRBC* units of packed red blood cells, *EBL* estimated blood loss, *OR time* operating room time, *NA* not available data, *LOH* length of hospital stay

[a] Primary and recurrent ovarian cancer patients

Table 5 Prognostic factors in patients undergoing secondary cytoreduction with liver resections for recurrent ovarian cancer

References	Number of patients	Univariate analysis	Multivariate analysis
Meredith et al. (2003)	26	Residual disease: <1 vs. >1 cm ($p = 0.031$) DFI: <12 vs. >12 months ($p = 0.004$) Distribution of disease: abdomen > pelvis or pelvis ≥ abdomen ($p = 0.028$)	NA
Yoon et al. (2003)	24	No significant prognostic factors found	NA
Loizzi et al. (2005)[b]	29	Histology ($p = 0.005$)[a] GOG PS at the time of the primary tumor diagnosis ($p = 0.031$)[a] Number of hepatic lesions ($p = 0.038$)[a] Presence of other sites of disease at the time of hepatic metastasis ($p = 0.033$) Treatment with platinum-based chemotherapy ($p = 0.011$)[a]	NA
Abood et al. (2008)	10	Size of largest metastatic tumor ≥5 cm ($p = 0.046$) Negative resection margin ($p = 0.024$)	NA
Pekmezci et al. (2010)	8		
Roh et al. (2011)	18	Distribution of disease: pelvis > abdomen or abdomen > pelvis ($p = 0.032$) Residual disease < or > 1 cm ($p = 0.0004$) Negative resection margins ($p = 0.0196$).	NA
Niu et al. (2012)	60	Residual disease < or > 1 cm ($p = 0.039$) Number of lesions ($p = 0.018$) DFI ($p = 0.018$)	Residual disease < or > 1 cm ($p = 0.039$)
Neumann et al. (2012)[b]	41	NA	Ascites ($p = 0.002$) Bilobular liver metastases ($p = 0.004$)
Kolev et al. (2014)	27	NA	DFI < vs. > 24 months ($p = 0.044$) Residual disease < or > 1 cm ($p = 0.014$)

DFI disease-free interval, *GOG PS* GOG performance status

[a] Referred to all the samples (not only hepatic metastatic ovarian cancer patients)

[b] Primary and recurrent ovarian cancer patients

diaphragm. The right dorsal area of the liver is in contact with the Gerota fat of the kidney, the adrenal gland, and the inferior vena cava (IVC), which are exposed after the coronary and triangular ligaments are divided. The IVC runs on the posterior side of the liver to the right side of the falciform ligament. Right, middle, and left hepatic veins drain in the IVC at the level where the peritoneum on the falciform ligament divides into right and left coronary ligament. The IVC is skeletonized, and the right lobe of the liver is fully mobilized, exposing all the peritoneal and hepatic surfaces.

Liver resections have been shown to be associated with less morbidity and mortality in high-volume centers (Nathan et al. 2009; Learn and Bach 2010). Depending on the complexity of the liver excision, this can be performed by the gynecologic oncologist or by a dedicated heptobiliary surgeon. Full liver mobilization and subdiaphragmatic peritoneal stripping and/or peritonectomy and non-anatomical hepatic resections, such as a wedge resection, can be performed by an experienced gynecologic oncologist. Anatomical hepatic resections have to be performed by a hepatobiliary surgeon.

Alternative approaches to liver metastases

Other local treatments for liver metastases, such as RFA and alcohol injection, have been proposed. However, data on these techniques are anecdotal.

Local ablation techniques were taken from the setting of surgically unresectable liver metastases from colon cancer, where reports on survival rates appear favorable. Current treatment strategies for colorectal liver metastases combine resection and local ablation techniques, such as RFA or microwave ablation, with the latter being used increasingly.

Through an electrode, RFA delivers high-frequency alternating current to the tissue surrounding the tumor, causing cell death. In EOC metastatic to the liver, the experience with the use of RFA alone is limited to case reports (Bleicher et al. 2003; Bojalian et al. 2004; Jacobs et al.

2003). The combination of RFA and excisional techniques has also been reported anecdotally (Mateo et al. 2005).

RFA and microwave ablation are effective local therapies that can be performed with minimal invasiveness. Local ablation can potentially be applied in patients with surgical or anesthetic contraindications leading to inoperability. The majority of percutaneous local ablations can be performed without the use of general anesthesia, especially if the liver lesions are not localized near the surface of the liver and Glisson's capsule. Another advantage of this local therapy is that it may be more beneficial if patients can recover quickly from them to allow for expeditious treatment with adjuvant chemotherapy. A disadvantage of local ablation is that it is associated with a higher recurrence rate compared to surgical excisions, and it is known from colorectal cancer surgery that lesions >3 cm are often suboptimally destroyed. Furthermore, the superficial hepatic lesions, which represent the largest amount of liver metastases in EOC, are treated by local ablation only if this is performed by open surgery, allowing for protection of surrounding tissues. Also, because of the risk of secondary biliary fistulae and sclerosis, these procedures should be avoided on metastases localized near the hilar region, where the large bile ducts are located. The precise effect of these techniques on survival rates remains speculative and should be offered only in highly selected cases.

Conclusions

In conclusion, hepatic resection for metastatic ovarian cancer is safe and is associated with a favorable outcome in highly selected patients (Table 2). In experienced hands, the resection of hepatic lesions does not increase the surgical complication rates of primary, interval, and secondary cytoreductive procedures (Table 1). Optimal cytoreduction, good performance status, negative resection margins, and long progression-free survival for recurrent patients are the most important prognostic factors predicting outcome (Table 3). Although some authors recommend that liver metastases in the ovarian cancer setting be divided into two groups based on the hematogenous spread or transcoelomic seeding, there are no clear criteria on how to define the metastatization pattern (Lim et al. 2009). Furthermore, from the data available in the literature, the complete resection of the lesion rather than the metastatization pattern seems to be important in determining outcome. Both at initial diagnosis and in the recurrent setting, liver resections should be performed only if a complete cytoreduction to no residual disease and negative resection margins can be achieved. Alternative physical and chemical local treatments of liver lesions should be offered only in highly selected cases.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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