Long-term Survivors After Liver Resection for Ovarian Cancer Liver Metastases

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Abstract. Ovarian cancer is one of the most aggressive gynecological malignancies and most patients are diagnosed at an advanced stage of disease. In these cases, the best therapeutic approach in order to provide good control remains an aggressive surgical approach leading to complete R0 resection. The experience provided by performing liver resection for colorectal hepatic metastases in association with the observation that residual disease remains the most important prognostic factor in ovarian cancer encouraged surgeons worldwide to include hepatic resection as part of the therapeutic armamentarium in ovarian cancer liver metastases. Patients and Methods: Data of patients submitted to liver resection for ovarian cancer liver metastases were retrospectively reviewed. The main inclusion criterion for the current study was a reported survival greater than 5 years after hepatic resection. Results: Eight patients were eligible for study inclusion: four cases were submitted to liver resection during primary cytoreduction, two cases were submitted to liver resection as part of secondary cytoreduction while the other two cases underwent hepatic resection at the moment of tertiary cytoreduction. In all cases R0 resection was achieved. Postoperatively one patient developed an abdominal abscess requiring for percutaneous drainage and one patient developed a hemoperitoneum necessitating re-operation. The mean overall survival was 123 months for patients submitted to liver resection as part of primary cytoreduction; patients submitted to liver resection as part of secondary cytoreduction experienced an overall survival of 66 and 73 months, respectively, while patients submitted to liver resection as part of tertiary cytoreductive surgery are alive at 5-year follow-up. Conclusion: In selected cases liver resection for ovarian cancer liver metastases can be associated with a significant increase of the overall survival.

Ovarian cancer remains one of the most aggressive gynecological malignancies being responsible for the highest number of gynecological cancer-related deaths (1). This aspect is especially related to the fact that most women are diagnosed in an advanced stage of the disease when distant metastases are already present. It has been widely demonstrated that ovarian cancer has a high capacity to induce distant metastases via the peritoneal, hematogenous and lymphatic route (2). Initially it has been considered that the presence of upper abdomen involvement is a sign of a tumor with a more aggressive biology and with a poorer outcome. However the improvement of surgical technique and success reported after resection of liver metastases from colorectal or neuro-endocrine primaries enabled surgeons worldwide to introduce liver resection as part of therapeutic armamentarium for advanced stage or relapsed ovarian cancer with hepatic involvement (3, 4). Although according to International Federation of Obstetrics and Gynecology (FIGO) classification there are two sub-types of liver metastases from ovarian cancer-peritoneal seeding and hematogenous seeding, studies so far, demonstrated that in both cases a significant advantage in terms of survival is expected if the principles of complete cytoreduction are applied (5-7).

Patients and Methods

After obtaining the approval of the Ethics Committee (no 153/2015) data of patients submitted to liver resection as part of debulking surgery for advanced stage or relapsed ovarian cancer at the ‘Dan Setlacec’ Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute, Bucharest were retrospectively reviewed. Patients eligible for the study were considered those who reported a greater than 60 months...
Liver resection as part of primary cytoreduction. The mean relapsed ovarian cancer. The goal of debulking surgery was an R0 resection, defined as no residual disease; residual disease between 0-1 cm was considered as R1 resection while cases in which residual disease larger than 1 cm was achieved, were classified as R2 resections. Liver metastases were considered as having hematogenous origin if the lesion was entirely surrounded by normal parenchyma while peritoneal seeding was incriminated if the liver lesion originated from the liver capsula and associated a parenchymal invasion of at least 2 cm. Minor hepatectomies were defined as liver resection of at least 2 segments according to Couinaud’s classification while resections of more than 2 segments were classified as major hepatectomies. The postoperative morbidity was classified according to Clavien-Dindo scale (8).

Results

Eight patients were considered eligible for the study. Four of the eight patients were submitted to liver resection as part of primary cytoreduction while the other four patients were submitted to liver resection as part of cytoreduction for relapsed ovarian cancer.

Liver resection as part of primary cytoreduction. The mean age at diagnosis of advanced-stage ovarian cancer was 52 years (range=42-60 years) while the initial FIGO stage was IIIC in one case and IV in the other three cases. In all cases preoperative imaging examination revealed the presence of a single liver lesion with diameter ranging between 2 and 4 cm. All cases were submitted to surgery with radical intent, an R0 resection being achieved in all cases. The main associated visceral resections consisted of total hysterectomy with bilateral adnexectomy in three cases, omentectomy, pelvic and parietal peritonectomy in four cases, pelvic and para-aortic lymph node dissection in one case and rectosigmoidectomy in one case; partial resection of the right diaphragm was also performed in one case. Case 4 had been initially submitted to total hysterectomy with unilateral adnexectomy twelve years previously for uterine leiomyoma and serous ovarian cyst. Twelve years later she presented for abdominal pain and weight loss and was diagnosed with an ovarian tumor on the remnant adnexa and bulky omental and peritoneal lesions. The patient was submitted to surgery in another surgical unit where an adnexectomy was performed; the patient was submitted to six cures of taxanes and platinum based chemotherapy. One month after ending the chemotherapeutic protocol she was re-submitted to surgery and total omentectomy, pelvic, parietal peritonectomy and atypical hepatectomy were performed, an R0 resection being achieved. All the other three cases were submitted to surgery as first intention therapy.

The main characteristics of the patients submitted to liver resection as part of primary cytoreduction are shown in Table I. The histopathological studies confirmed the presence of ovarian cancer liver metastases in all cases. The main pathological characteristics are summarized in Table II. The postoperative course was uneventful for cases 2, 3 and 4 while case 1 developed a Clavien–Dindo grade 2 complication, a mild pleural effusion that was successfully managed conservatively. The median hospital in stay was 11 days (ranging 9-16 days).

When it comes to long-term outcomes, the median overall survival was 123 months, all patients being dead of disease at the end of the study.

Liver resection as part of cytoreductive surgery for relapsed ovarian cancer. The other four cases were submitted to liver resection for ovarian cancer liver metastases in the setting of recurrent disease. Two of the four patients were submitted to liver resection as part of secondary cytoreduction. The patients had been diagnosed with FIGO stage IIIC and IC respectively at the ages of 48 and 49 years respectively. At the moment of initial diagnosis the patient with FIGO stage IIC disease was submitted to total hysterectomy, bilateral adnexectomy and omentectomy followed by six cycles of adjuvant chemotherapy and experienced a disease-free survival of 28 months. At the moment of first relapse she was directly submitted to surgery and a transverse colectomy, splenectomy, atypical hepatectomy, total peritonectomy and appendectomy were performed. Histopathological studies revealed the presence of a medium differentiated serous ovarian adenocarcinoma. The specimen of atypical hepatectomy showed the presence of a 4-cm unique liver metastasis with hematogenous origin while the specimen of splenectomy revealed the presence of capsular lesions invading the splenic parenchyma. The patient developed an intra-abdominal abscess which was successfully treated in a conservative manner (Clavien-Dindo grade 2 complication) and was discharged in the 12th postoperative day. Postoperatively she was submitted to six other cycles of taxanes and platinum-based chemotherapy and experienced a disease-free survival of 48 months; at that moment she was diagnosed with disseminated intra-abdominal lesions and was resubmitted to surgery with palliative intent. Finally she died of disease 66 months after secondary cytoreduction.

The second patient submitted to liver resection as part of secondary cytoreduction had been initially diagnosed with FIGO stage IC disease at the age of 49 years. At that moment a total hysterectomy and bilateral adnexectomy were performed followed by three cycles of adjuvant taxanes and platinum based chemotherapy. Four years later she was diagnosed with pelvic recurrence and hepatic isolated recurrence and was submitted to surgery with curative intent: the pelvic recurrence was resected en bloc with total cystectomy and rectosigmoidian resection while the liver lesion was resected by performing an atypical hepatectomy; an R0 resection was achieved. The histopathological studies revealed the presence of a 2-cm well-differentiated serous ovarian metastases with peritoneal origin. The postoperative course was uneventful the patient being
discharged in the 8th postoperative day. At 10 year follow-up after secondary cytoreduction the patient is alive with no signs of recurrent disease.

In both cases minor liver resections were performed. The patient died of disease 73 months after tertiary cytoreduction.

The other two patients were submitted to liver resection as part of tertiary cytoreduction for relapsed ovarian cancer. The patients had been diagnosed with FIGO stage IC and IIC disease respectively and submitted to tertiary cytoreduction at 74 and 82 months respectively. The first patient was diagnosed with an isolated liver metastasis at the moment of second relapse and was submitted to a major hepatectomy. The histopathological study confirmed the presence of a poorly differentiated serous ovarian adenocarcinoma liver metastasis with hematogenous origin. It was a unique liver metastasis measuring 4 cm with microscopically-negative resection margins. During the early postoperative course the patient developed a postoperative hemoperitoneum necessitating re-operation. At 5-year follow-up the patient reports no recurrent disease.

The last patient was initially diagnosed with FIGO stage IIC ovarian cancer and was submitted to tertiary cytoreduction at 82 months from the moment of diagnosis. At the moment of tertiary cytoreduction an R0 resection was achieved; the recurrences were resected en bloc with total cystectomy, splenectomy, parcelar gastrectomy and atypical hepatectomy. The histopathological studies of the specimen of hepatectomy revealed the presence of a 3 cm lesion with peritoneal origin, with negative resection margin. The postoperative course was uneventful, the patient being discharged in the 7th postoperative day. At 5-year follow-up she is alive with recurrent disseminated lesions and she was submitted to palliative chemotherapy.

**Discussion**

Hepatic resection has been proven a safe and effective method in treating colorectal liver metastases leading in time to a significant benefit in terms of survival when compared to cases treated by chemotherapeutic regimens only (3, 4). In the meantime, when it comes to ovarian cancer, it has been widely demonstrated that the only parameter which significantly and constantly influences the long-term survival is the completeness of resection, this fact being the only one which can be influenced by the surgeon. Progresses reported in the upper abdomen surgical technique and postoperative management leaded in time to an increase of the rate of cytoreduction to no residual disease even in cases with upper abdominal burden (9-11).

In the study conducted by Eisenhauer regarding the efficacy of the addition of upper abdominal surgery in order to achieve complete cytoreduction the authors included 262 patients with stages IIIC and IV ovarian cancers. The patients were submitted to surgery from 1998 to 2003 at the Memorial Sloan Kettering Cancer Center and were divided in three groups: the first group included patients submitted to cytoreductive surgery including upper abdomen procedures, the second group included cases with no upper tumoral burden in which complete cytoreduction was achieved after performing pelvic resections and the third group included patients with upper tumoral burden sub-optimally cytoreduced. Patients included in the first two
groups reported similar frequencies of achieving a complete clinical response, similar disease free survival intervals and similar overall survival rates. Oppositely to the first two groups, patients included in the third group reported significantly shorter disease-free survival and overall survival rates \( (p<0.001) \) although a faster recuperation and initiation of adjuvant chemotherapy was achieved. Liver resection was safely performed in 16% of cases in group 1, the rate of postoperative complications being similar between the three groups \( (p=0.54) \). The study came to demonstrate that the principles of debulking surgery can be safely applied in patients presenting upper abdominal tumor burden; in the meantime the authors demonstrated that the presence of upper abdomen involvement is not the distinctive sign of a poor tumor biology and significant improve of survival is expected if an R0 resection is performed \( (12) \).

Once it had been widely demonstrated that upper abdominal resections can be safely applied, with acceptable rates of postoperative complications and significantly improved survival, attention was focused on the role of liver resection as part of cytoreductive surgery for advanced-stage and relapsed ovarian cancer.

In the study conducted by Kolev et al. 76 patients submitted to liver resection for advanced-stage or relapsed ovarian cancer with hepatic involvement were included. Out of the 76 cases, 27 cases were submitted to liver resection as part of secondary cytoreduction. In 15 cases multiple hepatic lesions were found while in the other 12 cases isolated liver metastases were revealed. The main types of liver resection included segmentectomy (in 11 cases) and wedge resections (in 9 cases) followed by major resections such as multisegmentectomy (in 3 cases) and lobectomy (in 4 cases). The postoperative morbidity rate was 11%, three cases experiencing high-grade complications. The median overall survival after liver resection was 12 months \( (\text{range}=2-190 \text{ months}) \) and was significantly influenced by the interval from the first surgery \( (p=0.044) \) and the diameter of the residual disease \( (p=0.014) \) while the number of liver resection did not significantly impacted on survival \( (p=0.97) \) \( (13) \).

In order to demonstrate that a significant increase of survival can be achieved especially in patients with isolated liver lesions, Salih Pekmezci et al. included in their study eight patients with isolated hepatic metastases from ovarian cancer. The mean disease-free survival from the time of initial surgery to surgery for metastatic hepatic lesion was 5.38 years. The main surgical procedures performed were segmentectomy in three cases followed by left lateral sectorectomy and atypical hepatectomy, each in two cases and right hepatectomy in one case. The reported survival ranged between 7 months (the patient being dead due to sudden cardiac arrest) and 5 years (all four cases which were alive at 5-yearfollow-up had no evidence of recurrent disease). The authors reported a single patient who died three years after liver resection due to progression of the disease leading to multiple distant metastases. The authors concluded that a prolonged survival should be expected especially in cases with an initial long disease-free interval (between primary and secondary cytoreduction), this fact being an indicator of a good biological tumor behavior. In their opinion, another prognostic factor for a prolonged survival is the number of liver lesions, the presence of isolated ovarian cancer liver metastases being an important selection criterion \( (14) \). Similarly to Pekmezci’s study the long survivors identified in our study were in almost all cases patients with long disease-free intervals and isolated liver lesions.

Similar results were also reported by Sam Yoon’s study conducted on 24 patients with recurrent ovarian \( (21 \text{ cases}) \) or fallopian tube \( (3 \text{ cases}) \) carcinoma with liver involvement. The majority of patients experienced a slow tumoral progression from the moment of initial diagnosis (the median interval between primary diagnosis and hepatic resection being 68.5 months). At the time of diagnosis of liver metastases 17 cases presented a single liver lesion, 6 cases were diagnosed with two liver lesions and the last patient had five liver lesions. In six cases a liver-confined relapse was found, in 7 cases both liver and contiguous sites were revealed while in the other 11 patients both liver and non-contiguous site metastases were diagnosed. The main surgical procedures included segmentectomies (in 17 cases) followed by wedge resections (in 3 cases), lobectomies (in 2 cases) and trisegmentectomies (in the other 2 cases). The overall morbidity rate was 21% while the mortality rate was null; however a single patient developed a liver-related surgery complication – a bilioma. The authors reported a median overall survival of 62 months, three patients being alive at 5-year follow-up; two cases were reported to be alive with disease while the third patient had no evidence of disease 9 years after resection. The authors concluded that the ideal candidates for ovarian cancer liver metastases resection in which a maximal benefit in terms of survival is expected are those with favorable tumor biology (slow growing tumors, limited to liver recurrence or limited extra-hepatic disease, long disease free intervals) and with a good biological status. In the meantime the extent of liver resection (major versus
minor resection) and the dimension of the largest hepatic metastasis did not influence the outcome (15).

**Conclusion**

Hepatic resection for ovarian cancer liver metastases is a safe and effective surgical procedure successfully associated as part of debulking surgery for advanced and relapsed ovarian cancer. Long-term survival should be expected among patients with increased disease-free intervals and isolated recurrences. Although major hepatic resections might be needed, the magnitude of liver resection does not seem to influence the outcomes. When it comes to the pattern of spread a significant benefit in terms of survival was achieved for cases with both peritoneal and hematogenous lesions.

**References**


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