ONKOLOGIE

Surgery of Liver Metastasis in Gynecological Cancer – Indication and Results

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Summary
Background: Liver surgery for patients with liver metastases from gynecological malignancies, an indicator of advanced cancer disease, has remained unclear in the literature. We therefore analyzed the potential survival benefit of patients with surgically resectable compared to unresectable liver metastases. **Patients and Methods:** 43 patients who underwent surgery for liver metastases from gynecological cancers were included in our retrospective observational analysis. Overall survival was estimated according to the Kaplan-Meier method and compared with the log-rank test. **Results:** Primary gynecological tumors were breast (n = 27), ovarian (n = 8), and uterine (n = 8) cancers. Solely exploratory laparotomy was performed in 13 patients who served as controls. Whereas the perioperative mortality was 0%, minor complications occurred in 18.7%. The overall survival of all patients undergoing liver resection was significantly higher (p < 0.05) than that of patients with unresectable metastases. Subgroup analyses showed that particularly patients with respectable liver metastases from breast cancer had a significantly higher (50%) 5-year survival compared to patients with only an exploratory laparotomy. **Conclusion:** In selected patients, liver resection of metastases from gynecological cancers can achieve a survival benefit similar to that of patients with colorectal cancer metastases.

Zusammenfassung
Hintergrund: Die Rolle der Leberchirurgie bei Lebermetastasen gynäkologischer Tumoren ist bisher in der Literatur nicht geklärt. Aus diesem Grund haben wir untersucht, inwieweit Patienten mit resektablen gegenüber Patienten mit nichtresektablen Lebermetastasen einen Überlebensvorteil haben. **Patienten und Methoden:** In die retrospektive Analyse wurden 43 Patienten eingeschlossen, welche sich einer Operation bei Lebermetastasen ausgehend von gynäkologischen Tumoren unterzogen. Das Überleben der Patienten wurde anhand der Kaplan-Meier-Methode ausgewertet und mittels Log-Rank-Test miteinander verglichen. **Ergebnisse:** Die Patienten hatten als Primärtumor ein Mammakarzinom (n = 27), ein Ovarialkarzinom (n = 8) oder ein Uteruskarzinom (n = 8). In 13 Fällen konnte keine Leberresektion vorgenommen werden, und der Eingriff wurde als explorative Laparotomie beendet. Bei einer Mortalitätsrate von 0% traten bei 18,7% kleinere Komplikationen auf. Das Gesamtüberleben aller Patienten mit möglicher Leberresektion war signifikant größer (p < 0,05) als das der Patienten mit nichtresektablen Lebermetastasen. Die weitere Subgruppen-Analyse der Überlebensraten zeigte, dass insbesondere Patienten mit Mammakarzinom ein signifikant höheres (50%) 5-Jahresüberleben gegenüber den Patienten mit einer Exploration aufwiesen. **Schlussfolgerung:** Die Resektion von Lebermetastasen bei Patienten mit gynäkologischen Tumoren kann in selektierten Fällen mit einem Überlebensvorteil ähnlich dem bei Patienten mit Kolorektalkarzinommetastasen einhergehen. Daher sollte den Patienten im Rahmen einer multidisziplinären Anti-Tumortherapie eine Leberresektion in Kombination mit einer Chemotherapie angeboten werden.

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Introduction

Metastatic disease is the most common cause of death in patients with cancer [1]. Improved understanding of the hepatic anatomy together with technical advances during the last decades has enabled liver surgery to be performed with low mortality rates and minimal morbidity [2, 3]. Furthermore, modern surgical strategies from major hepatobiliary centers have demonstrated that hepatectomy of as much as 70% of the liver can be performed with a mortality rate of less than 5% [4, 5]. Until now, liver resection is the only curative treatment option for patients with colorectal liver metastases and intestinal endocrine tumors, as indicated by a 5-year survival of up to 50% [6–8]. Additionally, anatomic resections reduce the rate of positive tumor margins, and improve overall survival [9].

In contrast, in the literature, the role of liver resection for non-colorectal and non-endocrine liver metastases is not well defined. Historically, these patients with metastatic cancer would be given supportive or palliative treatment including chemotherapy [10]. The rationale against hepatectomy of liver metastases from non-colorectal and non-endocrine cancers is the likelihood of disseminated disease, as the liver is usually reached via the systemic circulation, and extrahepatic sites may have equal probability of being involved ('systemic disease') [11]. Interestingly, a recent multicenter study by Adam et al. [12] showed that liver resection for non-colorectal, non-endocrine metastases is becoming more prevalent.

In gynecological malignancies, metastasis to the liver is an indicator of advanced cancer disease [13]. In the literature, the efficacy of liver surgery for patients with liver metastases from gynecological cancers has remained unclear. Therefore, the aim of the present study was to evaluate the potential survival benefit of patients with surgically resectable compared to unresectable liver metastases.

Patients and Methods

Data from all patients were entered in a prospective database on an ISH-Med SAP platform (SAP, St. Leon, Germany). Between January 2000 and January 2007, 43 patients who underwent surgery for liver metastases from gynecological cancers were enrolled in the study. All patients with gynecological cancers had gynecological operations in combination with or without chemotherapy and radiotherapy prior to surgery for their liver metastases. All patients received antibiotic prophylaxis before surgery. After abdominal exploration, resectability of the liver metastases was verified using intra-operative ultrasound of the liver. The criteria for non-resectability were infiltration of vessel and biliary structures in the hilus, infiltration of all 3 liver veins, more than 10 liver metastases, and intraperitoneal metastasis. If liver resection was technically possible, partial hepatectomy was performed as an anatomic or atypical resection under Pringle maneuver or selective vascular clamping/occlusion. After liver resection, patients were transferred to the intensive care unit postoperatively. Data included all biographic and perioperative data as well as postoperative outcome. Survival of the patients was assessed retrospectively in November 2007.

Table 1. Characteristics and preoperative treatment of all patients (n = 43) with gynecological cancer undergoing liver resection (Phx) at our institution; mean ± standard error of the mean (SEM)

Age at the time of Phx, years	55.7 ± 1.3
ASA score	2.8 ± 0.2
Time between primary operation and Phx, months	76.9 ± 7.3
	Patients, n
Primary tumor sites	
Breast	27
Ovarian	8
Uterine	8
Pre-Phx chemotherapy/radiotherapy	
Breast	27/16
Ovarian	7/0
Uterine	3/4

Table 2. Intra- and postoperative course of all patients (n = 43) who underwent surgical procedures (n = 48) for liver metastases from gynecological cancer; mean ± standard error of the mean (SEM)

Operating time, min	153.6 ± 10.2
Blood loss, ml	325.7 ± 58.6
Postoperative hospital stay, days	9.4 ± 0.8
Postoperative stay on ICU, days	1.4 ± 0.2
Minor postoperative complications, patients, n	9
	Procedures, n
Liver resection procedures (n = 30 patients)	35
Repeat hepatectomy for hepatic recurrence (n = 4 patients) 5	
Exploratory laparotomy	13
Anatomic resection	20
Combined liver resection procedures (n = 11 patients)	12
Pringle maneuver	2
Selective vascular clamping or occlusion	10
Intraoperative transfusion (EC, FFP, TC units)	0

ICU = Intensive care unit; EC = erythrocyte concentrate; FFP = fresh frozen plasma; TC = thrombocyte concentrate.

Data are expressed as absolute numbers or mean ± standard error of the mean (SEM) unless indicated otherwise. The length of follow-up was calculated from the date of liver resection at our institution. Overall survival was estimated according to the Kaplan-Meier method and compared with the log-rank test using the software package SPSS 14.0® (SPSS GmbH Software, Munich, Germany).

Results

With respect to demographic data (table 1), the mean age of the women was 55.7 ± 1.3 years at the time of liver surgery. Primary tumor sites represented were breast (n = 27), ovarian (n = 8), and uterine (n = 8) cancers. Pre- and postoperative chemotherapy was used to treat primary tumors in 86% of the patients. The mean time from gynecological treatment of

Fig. 1. Overall survival of all patients with liver metastases from gynecological cancers. Patients with possible liver resection (black) had a significantly (p < 0.05) longer survival than patients who underwent an exploratory laparotomy only (white).
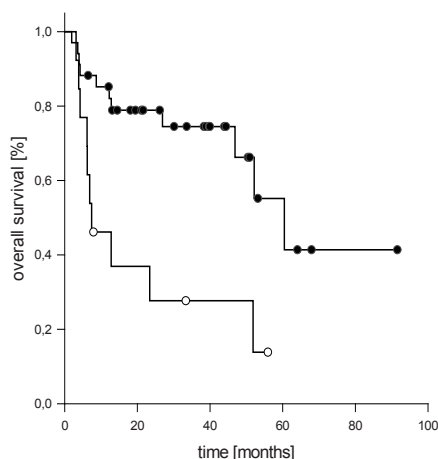
**Fig. 2.** Overall survival of patients with liver metastases from breast cancer. Patients with potential liver resection (black) were compared with those who received an exploratory laparotomy (white). Subgroup analyses showed that only patients with breast cancer metastases had a significantly longer survival after liver resection compared with controls undergoing exploratory laparotomy.
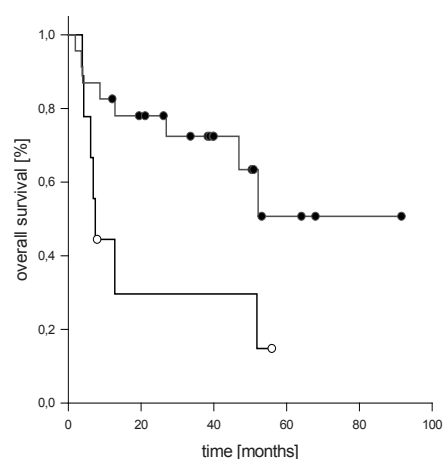
the primary tumor to liver resection was 76.9 ± 7.3 months. No neoadjuvant chemo/radiotherapy for liver metastases was performed. The 3 patients with synchronous liver metastases received liver surgery within 4–6 weeks after the gynecological operation for breast cancer. A total of 3 patients – 2 patients with breast cancer and 1 patient with ovarian cancer – had synchronous liver metastases. All other patients had metachronous disease. The distribution of the liver metastases was uni- and/or bilobular. At the time of liver surgery, only 1 patient with ovarian cancer metastases had extrahepatic disease. The peritoneal metastases of this patient were resected during the same operation. No liver resection could be performed in 13 patients, and the operation was ended as an exploratory laparotomy (table 2). Four patients with recurrent liver metastasis of breast cancer had a repeat hepatectomy, 1 patient even two repeat hepatectomies. Anatomic resections based on the segments defined by Couinaud were performed in 57% of patients. Major hepatectomy, defined as resection of more than 2 anatomic segments, was required in 25% of the patients. Atypical and anatomic resections were performed as single or combined procedures (n = 12 combined multiple liver surgery procedures). Within 35 liver resection procedures performed in 30 patients, a total number of 79 liver metastases were resected. The perioperative mortality was 0%. Only minor complications occurred in 18.7% of the 48 operations including e.g. urinary infection, pneumonia, and cholangitis. The mean postoperative hospitalization was 9.4 ± 0.8 days. Histologically, 3 patients with liver resections of metastases from breast cancer had an R1 resection margin. One patient with breast cancer metastases was left with an R2 situation after liver resection, and was treated intra-operatively with cryotherapy of the resection margin. All other patients with liver resection procedures (n = 31) had an R0 resection margin. Patients with liver metastases from ovarian cancer received adjuvant chemotherapy after liver surgery.

After a mean follow-up interval of 29.4 ± 3.6 months, the overall 5-year survival for the entire cohort was 30% with a median overall survival of 51.8 months. The overall survival of patients undergoing liver resection was significantly higher (p = 0.002) than that of patients who received only an exploratory laparotomy (fig. 1). Patients with liver metastases from primary breast tumors represented the largest subset in our series (n = 27). Following hepatic resection, these patients experienced 5-year survival of 50% which was significantly higher (p = 0.018) compared to patients with only an exploratory laparotomy (median survival of 7.4 months (fig. 2)). Subgroup analysis of patients with liver metastases from ovarian and uterine cancers showed no significant differences between patients with resectable liver tumors and unresectable liver tumors. Furthermore, analysis of all patients with liver metastases from non-breast primary tumors showed longer survival of patients with possible liver resection compared to patients with exploratory laparotomy only, but these data did not reach statistical significance (p = 0.063). In the case of intrahepatic recurrence, 4 of 27 patients with liver metastases from breast cancer underwent a second hepatectomy, and one of these 4 patients re-recurred in a resectable pattern, and underwent a 3rd hepatectomy. Following repeated hepatectomy, these 4 patients had a mean survival time of 52.9 months, comparable with a mean survival time of 57.1 months of patients after a single hepatectomy.

Discussion

The major finding of the present study is that patients with liver metastases from gynecological cancers have a survival benefit whenever liver resection is possible, especially in cases with breast cancer. In the present study, comparable to previously published data [2, 3], liver resection was safe for the patients, with no perioperative deaths and an acceptable minor complication rate. Our study focused only on liver metastases from gynecological cancers, which are not a common indication for liver resection. Because different primary tumor types have different underlying tumor biology, the ideal study should

concentrate on only one tumor type. However, with regard to the low number of patients, this is difficult [12, 14–19].

Liver surgery in breast cancer patients is viewed controversially in the literature. On the rationale of oncologists, breast cancer is a 'systemic disease'. In contrast, as shown by Adam et al. [11], liver resection provides a significant survival benefit over medical therapy alone for patients with breast cancer liver metastases. Analyzing their 108 patients with diagnosis of hepatic metastases from breast cancer, the study group identified response to preoperative chemotherapy, positive resection margin, and repeated hepatectomy for intrahepatic recurrence as independent prognostic factors. According to the reported overall 37% 5-year survival, we demonstrated in the present study a similar overall 5-year survival of 50% for patients with breast cancer alone.

Our data showed that aggressive intervention with liver resection for metastases from gynecological cancers was associated with a beneficial 50% 5-year survival after partial hepatectomy. These findings are comparable to previous data by Adam et al. [12], which demonstrated a 5-year survival rate after resection of liver metastases from ovarian tumor sites of 50%, from breast cancer of 41%, and from uterine primaries of 35%. Interestingly, our data showed a significant benefit from liver resection compared to unresectable controls. Because our data represent a selection of patients undergoing liver surgery and there is no randomized control group, this uncertainty could lead to the hypothesis that the role of hepatic surgery for this group is cytoreduction only in chemotherapy-responsive tumors. As we know from the literature [13], in ovarian cancer, surgical cytoreduction of intraperitoneal disease has a substantial effect on survival, whether performed as a primary treatment, interval debulking, or secondary debulking for recurrent cancer. In this type of gynecological cancer, survival of patients with partial hepatectomy is similar to that of patients without liver disease but with similar volumes of residual cancer [20–21]. In these cases, only a longer disease-free interval remained a prognostic factor [13].

As shown in the present study, liver resection of metastases from gynecological cancer can achieve a survival benefit similar to that of patients with colorectal cancer metastases. Taken together, these findings could only be observed if each liver metastasis of gynecological cancers could be removed. Additionally, previous studies in patients with non-colorectal metastases showed that prognostic indicators for the survival of these patients after partial hepatectomy are the type of liver resection and complete tumor resection (R0) [12, 14–19]. Furthermore, for the first time, our data did not demonstrate any significant difference with respect to the type of gynecological cancer. This differs from the results of others [12, 14–19] who have identified primary tumor type as an important prognostic factor. Unfortunately, no direct correlation to our analysis is possible, because these studies include liver metastases from all types of non-colorectal cancers.

In conclusion, with the very low mortality rate of liver resection, oncologists and surgeons should offer patients with liver metastasis from gynecological cancer a multimodal multidisciplinary anti-cancer treatment approach including liver surgery and chemotherapy.

Acknowledgement

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