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Original research

Hepatic resection of non-colorectal and non-neuroendocrine liver metastases – Survival benefit for patients with non-gastrointestinal primary cancers – A case-controlled study

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ABSTRACT

Purpose: Whereas resection of colorectal liver metastases is gold standard, there is an ongoing debate on benefit of resection of non-colorectal (NCRC) and non-neuroendocrine (NNEC) liver metastases.
Methods: The potential survival benefit of patients undergoing resection of NCRC or NNEC liver metastases was investigated. Data from a prospectively maintained database were reviewed over a 7-year period. Kaplan–Meier method was used for the evaluation of outcome following resection.
Results: 101 patients underwent 116 surgical procedures for synchronous and metachronous NCRC or NNEC liver metastases with a morbidity of 23% and a mortality of ~1%. 11 patients underwent repeated liver resection procedures. Overall 5-year survival after liver resection was 30% depending on primary tumour site. Median survival was significantly increased after resection of hepatic metastases from non-gastrointestinal primaries compared to gastrointestinal primaries. Resection of hepatic metastases from non-gastrointestinal primaries resulted in significantly increased median survival compared to exploration only. Patients with hepatic metastases from gastrointestinal primaries did not benefit from hepatic surgery.
Conclusion: Hepatic resection for liver metastases from NCRC or NNEC cancers is a save treatment procedure. However, the decision to perform surgery should depend on the primary cancer. Especially patients with liver metastases from non-gastrointestinal primaries profit from hepatic surgery.

1. Introduction

Liver resection for the treatment of distant cancer metastases is a well established therapy option which has been introduced in the middle of the past century.[1] As a result of improved knowledge of liver anatomy and physiology[2] as well as modern surgical techniques and intensive care treatment strategies, hepatic surgery for liver metastases has become a safe procedure with low mortality.[3,4] Whereas the prognosis of untreated liver metastases from colorectal cancer is very poor with a median survival of less than 12 months,[5] resection of colorectal liver metastases representing the only curative treatment option improves the prognosis to a 5-year survival rate of ~40%[6] and 10-year survival rates of up to 25%.[7,8] Furthermore, aggressive surgical therapy of neuroendocrine liver metastases has recently been demonstrated to improve clinical symptoms and increase survival rates up to 83% after 3–5 years.[9–12]

In contrast, there is an ongoing debate on the indication for resection of hepatic metastases from non-colorectal (NCRC) and non-neuroendocrine (NNEC) primary tumours. In such patients, metastases reach the liver via systemic circulation, and thus a systemic tumour spread has to be assumed. Therefore, systemic chemotherapy has been recommended for these patients in the past. Furthermore, the group of patients with isolated liver metastases from NCRC and NNEC is found to be small in number and very heterogeneous due to a large variety of underlying primary tumours. Consequently, there is a huge diversity of palliative chemotherapy regimes for the treatment of liver metastases from the different primaries, at least leading to a median survival of 24–27 months in slow-growing cancers, such as renal cell carcinomas

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or breast cancer.[13,14] In contrast, for pancreatic[15] or gastric cancers,[16] chemotherapy has shown to be ineffective as survival is only prolonged by a few weeks. The issue of liver metastases surgery for NCRC and NNEC is clinically important. In parallel to therapy of colorectal cancer, cryosurgery or radio frequency ablation have been discussed as minimally invasive local approaches in systemic NCRC or NNEC tumour disease,[17,18] but these therapies are not established as standard treatment options for NCRC or NNEC liver metastases yet. However, some recently published reports suggest that patients with liver metastases from NCRC and NNEC carcinoma might benefit from hepatic resection.[19–22] A recently published overview by Lehner et al. showed a 5-year survival rate of 27–39% in patients undergoing liver resection of NCRC and NNEC metastases.[4] Interestingly, there are diverging results showing a clear-cut impact of the localisation of the primary tumour on the respective survival rates.[4,20]

Thus, the aim of the present study was to analyse the benefit of liver resection for NCRC and NNEC hepatic metastases in the patient collective of our large hepatobiliary referral centre. Furthermore, the intent of the present study was to investigate if the surgical approach for resectable liver metastases of NCRC and NNEC origin is an effective strategy to prolong survival compared to palliative treatment regimes and to emphasize the value of surgery in multimodal therapy concepts.

2. Patients and methods

2.1. Data acquisition

Data from all patients undergoing hepatic surgery were prospectively entered in an i.s.h.-med database (GSD, Berlin, Germany) running on a SAP platform (SAP, St Leon-Rot, Germany). For this cohort study, data from patients undergoing liver resection for NCRC and NNEC metastases in a 6-year period were retrieved from that database and analysed retrospectively. Thus, for all patients all data for any variable were available.

2.2. Inclusion criteria for surgery

In all patients, resection of the primary cancer was categorized to be formally curative as defined by removal of all macroscopically detectable tumour and microscopically clear resection margins. Operations on the primary tumour were performed in combination with or without chemotherapy and radiotherapy using neoadjuvant and adjuvant protocols. Histological classification was performed according to international standards.[23] All patients undergoing liver resection had a standardised general anaesthesia including epidural analgesia, balanced volume status and prophylactic perioperative antibiotics. In our retrospective study, all patients presenting at our hepatobiliary centre for resection of hepatic metastases from NCRC or NNEC primaries were included. The decision on operability was based on patients' performance status, declared patients' will, and informed consent. Further, resectability as well as choice of the operative procedure – selected to ensure both adequate oncological resection margins and a maximal volume of functional hepatic parenchyma remnant – were based on preoperative diagnostics, i.e. CT scan or magnetic resonance tomography. Findings after laparotomy and intraoperative ultrasound were the final criteria for resection of hepatic metastases or exploration only in case of non-resectability. Criteria for non-resectability were infiltration of all three liver veins, diffuse liver metastases and non-resectable extrahepatic tumour manifestations, either detected in preoperative imaging or as intraoperative finding. Synchronous or metachronous state of the metastases as well as number, location (uni-lobular or bi-lobular) or size of the metastases were no exclusion criteria for surgical exploration.

2.3. Surgical procedures and postoperative follow-up

Partial hepatectomy was performed as anatomical resection according to Couinaud,[2] as non-anatomical or wedge resection and as a combination of anatomical and non-anatomical resections with or without Pringle's manoeuvre, selective vascular clamping or selective vascular occlusion. Major hepatectomy was defined as resection of three or more anatomical liver segments.[24] Tissue destruction within the parenchymal dissection line was usually performed by ultrasonic dissection and the resection margins of the remnant liver were coagulated by argon plasma beamer. Complete lymph node dissection of the hepatoduodenal ligament was performed when size and firmness of the lymph nodes were suspicious for malignant infiltration.

Data was recorded prospectively in our database including all demographic details, disease-related data, medical data and data from the peri-operative and postoperative course. Recurrence and follow-up information from the patients was determined from the medical records or was assessed retrospectively. Follow-up examinations included CT-scan or magnetic resonance tomography every 6 months after hepatic surgery for liver metastases.

2.4. Statistical analyses

Data is expressed as absolute numbers, percent, 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 with a median of 18 months. Comparisons of categorical and continuous variables were performed using the χ^2-test, Fisher's exact test if applicable and the Wilcoxon rank-sum test. Differences between more than two groups were calculated by ANOVA followed by the recommended post-hoc test. To clarify and structure our data, patients with neoadjuvant treatment of liver metastases before liver surgery in our centre and loss of follow-up were excluded from univariate and survival analyses. Survival analyses were estimated according to the Kaplan–Meier method and compared with the long-rank test using the software package SPSS 14.0® (SPSS GmbH Software, Munich, Germany). Patients who died from unknown cause of death were also counted as an 'event' in the Kaplan–Meier analysis as well as other patients who died from tumour recurrence. P values of <0.05 were considered significant.

3. Results

3.1. Patient demographics

101 patients underwent a total of 116 surgical procedures for liver metastases from NCRC or NNEC primary cancers, including 24 explorations only. Our cohort comprised 57 female (56.4%) and 44 male (43.6%) patients with a mean age of 58.6 ± 1.1 years at time of liver surgery, among which 20.8% were older than 70 years (Table 1).

Regarding the primary tumour, T stages 1–3 were found in similar frequency, precise T staging could not be determined in 28 patients. 26.7% of the patients had synchronous hepatic metastases, defined as liver metastases occurring within 6 months after diagnosis of the primary tumour. 48 patients had adjuvant chemotherapy for the respective primary tumour, and 10 underwent chemotherapy even before liver surgery (Table 1).