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The role of hepatectomy for synchronous liver metastases from pancreatic adenocarcinoma

Andreas Andreou[a,*], Sebastian Knitter[a,d], Fritz Klein[a], Thomas Malinka[a], Moritz Schmelzle[a], Benjamin Struecker[a,d], Rosa B. Schmuck[a,d], Alina Roxana Noltsch[a], Daniela Lee[a], Uwe Pelzer[b], Timm Denecke[c], Johann Pratschke[a], Marcus Bahra[a]

[a] Department of Surgery, Charité – Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow Klinikum, Germany
[b] Department of Hematology, Oncology and Tumor Immunology, Charité – Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow Klinikum, Germany
[c] Department of Radiology, Charité – Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow Klinikum, Germany
[d] Berlin Institute of Health (BIH), Berlin, Germany

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ABSTRACT

Background: The role of hepatectomy for patients with liver metastases from ductal adenocarcinoma of the pancreas (PLM) remains controversial. Therefore, the aim of our study was to examine the postoperative morbidity, mortality, and long-term survivals after liver resection for synchronous PLM.

Methods: Clinicopathological data of patients who underwent hepatectomy for PLM between 1993 and 2015 were assessed. Major endpoint of this study was to identify predictors of overall survival (OS).

Results: During the study period, 76 patients underwent resection for pancreatic cancer and concomitant hepatectomy for synchronous PLM. Pancreatoduodenectomy, distal pancreatectomy, and total pancreatectomy were performed in 67%, 25%, and 8% of the patients, respectively. The median PLM size was 1 (1–13) cm and 36% of patients had multiple PLM. The majority of patients (96%) underwent a minor liver resection. After a median follow-up time of 130 months, 1-, 3-, and 5-year OS rates were 41%, 13%, and 7%, respectively. Postoperative morbidity and mortality rates were 50% and 5%, respectively. Preoperative and postoperative chemotherapy was administered to 5% and 72% of patients, respectively. In univariate analysis, type of pancreatic procedure (P = .020), resection and reconstruction of the superior mesenteric artery (P = .016), T4 stage (P = .086), R1 margin status at liver resection (P = .001), lymph node metastases (P = .016), poorly differentiated cancer (G3) (P = .037), no preoperative chemotherapy (P = .013), and no postoperative chemotherapy (P = .005) were significantly associated with worse OS. In the multivariate analysis, poorly differentiated cancer (G3) (hazard ratio [HR] = 1.87; 95% confidence interval [CI] = 1.08–3.24; P = .026), R1 margin status at liver resection (HR = 4.97; 95% CI = 1.46–16.86; P = .010), no preoperative chemotherapy (HR = 4.07; 95% CI = 1.40–11.83; P = .010), and no postoperative chemotherapy (HR = 1.88; 95% CI = 1.06–3.29; P = .030) independently predicted worse OS.

Conclusions: Liver resection for PLM is feasible and safe and may be recommended within the framework of an individualized cancer therapy. Multimodal treatment strategy including perioperative chemotherapy and hepatectomy may provide prolonged survival in selected patients with metastatic pancreatic cancer.

1. Introduction

Despite recent advances in the multimodal treatment of patients with pancreatic ductal adenocarcinoma (PDAC) [1–3], therapeutic management still poses a challenge and long-term survival remains often unsatisfactory [4]. While clinical symptoms are indistinct and impede diagnosis of pancreatic cancer, advances in imaging techniques offer precise detection of tumor location and extent, enabling detailed planning of individualized treatment for each patient [5]. In this regard, surgical resection with curative intent is currently considered to be the only chance for long-term survival [6,7]. Over the last decades, progress in surgical techniques and improvements in the perioperative setting have allowed for continuously decreasing morbidity and mortality rates following pancreatic cancer surgery in high-volume centers

* Corresponding author. Department of Surgery, Campus Charité Mitte and Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353, Berlin, Germany.
E-mail address: andreas.andreou@charite.de (A. Andreou).

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[8]. However, only a subset of 10–20% of patients with PDAC is eligible for curative intended resection due to locally advanced disease or early tumor spread while resection margins are frequently positive for tumor cells (R1) following histological examination of the surgical specimen [9,10]. As most common site of tumor dissemination, up to 70% of patients present with liver metastases from ductal adenocarcinoma of the pancreas (PLM) at time of diagnosis or develop PLM in the course of their disease [7]. These findings usually lead to a palliative treatment recommendation and preclude patients from potentially curative surgery according to current national and international guidelines [11,12]. Despite of this, highly selected patients with PLM may benefit from a combined surgical approach including pancreatic surgery with concomitant resection for PLM [13,14]. Pursuing resection for PDAC and synchronous PLM, outcomes were still poor in previous studies and thus the benefits of this approach remained controversial [15,16].

Therefore, objective of this study was to evaluate the overall survival (OS) of patients undergoing pancreatic surgery and concomitant hepatic resection for synchronous PLM and identify predictors associated with worse OS. Additionally, we assessed the postoperative morbidity, mortality, and disease-free survival (DFS) in this patient cohort.

2. Materials and methods

2.1. Patient inclusion criteria

Following approval by the Institutional Review Board (EA2/035/14), clinicopathological data of 76 consecutive patients who underwent resection for pancreatic cancer and concomitant hepatectomy for synchronous PLM between 1993 and 2015 in our center were collected. Only patients with pancreatic adenocarcinoma who underwent pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy with curative intent were included in the analysis. Safe removal of all radiologically evident disease defined curative surgical eligibility. Patients presenting with inoperable extent of disease and those with palliative treatment intent were excluded from the analysis.

2.2. Preoperative assessment

Standard preoperative patient evaluation included medical history, physical examination, serum laboratory tests, imaging studies, and an anesthesia evaluation. The location and extent of tumor burden as well as the presence of lymph node or distant metastases were determined by cross-sectional imaging such as computer tomography with triphasic contrast agent protocol or magnetic resonance imaging. If necessary, fluorodeoxyglucose-positron emission tomography or diagnostic laparoscopy was performed. All patients were presented at a multidisciplinary tumor board including hepatopancreaticobiliary (HPB) surgeons, medical oncologists, and specialized radiologists. Tumor resectability was discussed and an individualized course of treatment was established for each patient. In case of preoperatively detected PLM, liver resection was considered, if safe removal of PLM was possible and the liver remnant was deemed sufficient.

2.3. Surgical procedure

In this study, pancreatic resections included pancreatoduodenectomy, distal pancreatectomy, and total pancreatectomy. After transverse upper laparotomy, previously undiagnosed tumor spread was determined by examination of the peritoneal cavity whereas intraoperative ultrasonography of the liver was used for confirmation and localization of PLM. In accordance to a previous national multicentric study [17], classic Kausch-Whipple or pylorus-preserving pancreatoduodenectomy was performed to remove the pancreatic head followed by a pancreatogastrostomy connecting the pancreatic remnant to the dorsal gastric wall or a pancreatojejunostomy using a dissected jejunal loop. End-to-side hepaticojejunostomy was performed to reconstruct the remaining bile duct. Gastrointestinal passage was reestablished by Roux-en-Y gastrojejunostomy. Perianastomotic drains were intraoperatively put in place allowing monitoring for pancreatic fistula, anastomotic leaks, and postoperative hemorrhage.

The Brisbane 2000 terminology of liver anatomy was used to describe the extent of hepatectomy. Resection of 3 or more liver segments according to Couinaud's classification defined major hepatectomy [18].

2.4. Postoperative management

After surgery, all patients were admitted to a specialized intensive care unit and were monitored for postoperative complications including anastomotic leak, pancreatic fistula, bleeding, intraabdominal infection, and organ failure. Nasogastric decompression and nil per os diet were routinely administered after pancreatoduodenectomy until a contrast agent swallow exam excluded an anastomotic leak and thus allowed for switching to an oral diet. Increased discharge through perianastomotic drains, or increased bilirubin and lipase levels in drained fluids were used as indicators for biliary leak, pancreatic fistula, or anastomotic leak. The criteria of the International Study Group on Pancreatic Fistula were used for classifying postoperative pancreatic fistulas (POPF) in three severity grades (A, B, or C) and patients were treated accordingly [19]. The perianastomotic drains were removed if the discharge was qualitative unremarkable and less than approximately 500 cc per day.

Postoperative morbidity and mortality was defined as any complication or death within 90 days after the surgical procedure, respectively. Major complications included all events requiring endoscopic, radiological, or surgical intervention and complications resulting in a life-threatening condition requiring organ support measures.

Postoperative chemotherapy was offered to patients based on recommendations of the interdisciplinary tumor board.

2.5. Histological evaluation

Routine histopathological evaluation of the resected tissue was performed to confirm the tumor entity of the primary tumor and the liver lesion and describe the tumor stage according to the TNM classification. If surgical resection margins were microscopically free of tumor cells for > 1 mm, R0 resection was defined, as previously described [20].

2.6. Statistical analysis

Quantitative and qualitative variables were expressed as medians (range) and frequencies. Primary endpoint of the study was OS and secondary endpoints were postoperative morbidity, postoperative mortality, and DFS. Using the Kaplan-Meier method, OS was calculated from the date of surgical procedure to the date of death or last follow-up and DFS was calculated from the date of surgery to the date of recurrence or last follow-up. Log-rank tests were used to assess significance for univariate analyses.

To identify factors associated with OS and DFS after pancreatic resection and concomitant hepatectomy for synchronous PLM, the following clinicopathological variables were analyzed: sex, age, type of pancreatic procedure, resection of portal vein, resection of superior mesenteric artery, T-stage, regional lymph node status, tumor grading, venous invasion, lymphangiosis carcinomatosa, resection margin status at pancreatic resection, major hepatectomy, number of PLM, resection margin status at liver resection, preoperative chemotherapy, postoperative chemotherapy, postoperative morbidity, postoperative pancreatic fistula, and insufficiency of biliary anastomosis. In the subsequent multivariate analysis, all factors with P value $< .1$ in univariate analysis were entered in a Cox regression model with backward elimination. P values $< .05$ were considered statistically