

ORIGINAL ARTICLE

Multicentre study of the impact of factors that may affect long-term survival following pancreaticoduodenectomy for distal cholangiocarcinoma

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Abstract

Background: Although the peri-operative mortality following pancreaticoduodenectomy (PD) for distal cholangiocarcinoma (DCC) has decreased, the post-operative morbidity remains high. The aim of this study was to evaluate the impact of factors that may affect the long term survival for patients with DCC following PD.

Methods: All patients who underwent PD for DCC between January 2000 and December 2015 in 5 tertiary referral centers underwent retrospective medical record review. Factors likely to influence overall (OS) and disease-free (DFS) survivals were assessed by univariate and multivariate analysis.

Results: A total of 201 on 217 patients who underwent PD for DCC were included for further analysis. The median OS was 39 months, with actuarial survival rates at 1, 3, and 5 years of 85%, 53% and 39%. Recurrence occurred in 123 (61%) patients. The median DFS was 16 months, with actuarial survival rates at 1, 3 and 5 years of 60%, 37% and 28%. Following multivariate analysis, peri-operative blood transfusions (PBT) were associated to worse OS (HR = 2.25 [1.31–3.85], $P = 0.003$) and DFS (HR = 2.08 [1.24–3.5], $P = 0.005$).

Conclusion: This study confirms the negative impact of PBT on the oncologic result following PD for DCC.

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Introduction

The only potentially curative treatment of distal cholangiocarcinomas (DCC) is an oncologic pancreaticoduodenectomy (PD), yielding a 5-year overall survival (OS) rate less than 30% and a median OS of 37 months.¹ This prognosis is closely related to local recurrence and metastatic spread, which require an appropriate treatment.² Therefore increased understanding of the risk factors of recurrence is fundamental to improve long term outcomes.

The post-operative mortality following PD is decreasing, due to improvements in peri-operative care, surgical techniques and centralization to high-volume institutions.^{3,4} However despite

these improvements, the post-operative morbidity remains high, from 30% to 50%.⁵ This morbidity is particularly linked to delayed gastric emptying (DGE), pancreatic and biliary fistulae, intra-abdominal infection and hemorrhage.⁶ Control of these complications depends on optimal preparation of the patient, meticulous and standardized operative technique, careful post-operative monitoring, early and appropriate management of complications.⁷ Recent evidence has shown that enhanced recovery after surgery protocols decrease hospital stay following PD, particularly in elderly patients.^{8,9}

To date, few studies with a small number of patients have focused on post-operative morbidity after PD for patients with

DCC. The aim of this multicenter study was to examine the effect of factors that may affect long term outcomes following PD in patients presenting with DCC.

Methods

All consecutive patients who underwent PD for DCC in 5 tertiary referral centers between January 2000 and December 2015 were extracted from prospective maintained databases and were analyzed retrospectively. Only patients with pathologically confirmed DCC were included. Pancreatic, ampullary and duodenal carcinomas were excluded from the analysis. This work was conducted after approval by the institutional review boards.

The data collected included demographics (age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score,¹⁰ tumor type, lymph node status, duration of surgery, venous or arterial resection and reconstruction, concomitant abdominal surgery, and peri-operative allogenic blood transfusion (PBT)), defined by the necessity of transfusion during the surgery or the hospitalization period. Post-operative pancreatic fistula was classified according to the International Study Group of Pancreatic Fistula (ISGPF) classification and only grades B and C were considered as recently recommended.^{11,12} Delayed gastric emptying (DGE) were classified according to the International Study Group of Pancreatic Surgery classification (ISGPS).¹³ In this study, only DGE of grades B and C were considered. Post-pancreatectomy hemorrhage, including intra- and extraluminal hemorrhage were classified as per the ISGPS.¹⁴ Biliary fistula, was defined as the presence of bile in the drain fluid. Systemic infections were defined as the presence of infectious signs requiring the administration of systemic antibiotics. Post-operative complications were classified according the Clavien-Dindo classification system.¹⁵ Major complications were defined by a complication \geq IIIB in Clavien-Dindo classification. Peri-operative mortality was defined as death during the initial hospital stay. Mortality during the 30 and 90 postoperative days was also documented.

Surgery

All PD were performed following the standard Whipple procedure and Child reconstruction (using pancreaticojejunostomy), by senior pancreatic surgeons. All patients had intraoperative frozen section examination of the proximal main bile duct and the pancreatic section of the specimen. If invaded, additional resection to achieve a negative margin was performed. During reconstruction, pancreatic duct intubation was left to the discretion of the operator, but was generally performed in patients with small duct size (<3 mm) or soft pancreatic texture.

Pathology

The histological diagnosis was established by an expert pathologist in biliopancreatic disease according to the macroscopic and microscopic aspect and immunohistochemistry (with cytokeratin

7 and 20) in all patients. When distinction between DCC and others peri-pancreatic malignancies was questionable, specimen was reviewed by a second pathologist and patients were only included if there was agreement. Considering the microscopic margin involvement, pathologists used a definition based on a 1 mm clearance, to specify R0 resection.

Follow-up protocol

After resection, adjuvant chemotherapy was discussed in a multidisciplinary collaborative meeting. All patients were followed every 3 months. A computed tomography scan was systematically performed every 3 months during the first 2 years after surgery and every 6 months thereafter. Follow-up data were obtained through routine clinical visits or through personal contact. Patients who died during the first 90 post-operative days were excluded from the survival analysis. The end of follow-up was between September 2017 and October 2017 or at the time of death.

Recurrence

Recurrence was considered when new lesion was shown on imaging finding without histological confirmation. When recurrence was diagnosed, the treatment strategy was determined at a multidisciplinary collaborative meeting, which was attended by pancreatic surgeons, radiologists, oncologists and gastroenterologists. According to their general condition and the degree of disease extension, the patients were treated with chemotherapy, using gemcitabine or gemcitabine plus oxaliplatin (GEMOX), radiation therapy or hepatic radiofrequency ablation. For localized non-progressive liver metastases, the feasibility of radiofrequency ablation and surgical resection were systematically discussed.

Statistical analysis

Quantitative variables are expressed as medians and inter quartile range (IQR) and qualitative variables are expressed as numbers and percentages. Survival analysis was performed by Kaplan–Meier curve analysis and the results were compared with the log-rank test. All variables with $P < 0.10$ by univariate analysis were entered into a multivariate model (i.e., COX proportional hazard model). The best final multivariate model was selected using a stepwise method in order to only retain variables with a P value of <0.05 . To appreciate the accuracy of the final Cox model (both for OS and DFS), the Harrell's C-index were calculated. The absence of collinearity effect between variables was appreciated by calculation of the variance inflation factor in each best final selected model. All statistical analyses were performed using R statistical software, version 2.15.1 (<http://www.r-project.org/>).

Results

During the study period, 201 (93%) patients on 217 patients who underwent PD with curative intent for DCC were included for

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