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ORIGINAL ARTICLE

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).

Conclusions: 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 Anaesthesiologists (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 necessary 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 ≥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 gemcitabin or gemcitabin 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 appreciate 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 further analysis (Supplementary Figure 1). Peri-operative variables are shown in Table 1. All patients had tumor free proximal bile duct margin, after frozen section analysis. Short term post-operative outcomes are shown in Table 2. Reoperation was needed in 42 (19%) patients. The 90 day mortality rate after surgery was 7% (n=16). After surgery, 65 (30%) patients received adjuvant therapy, mostly chemotherapy regimen alone, of which 8 (12%) patients had already received neoadjuvant chemotherapy.

The median follow-up was 24 [15-48] months. At the end of the study, 117 (58%) patients were dead and 35 (16%) patients were lost to follow up. The overall median survival (OS) was 39 months, and actuarial OS at 1, 3 and 5 years was 85%, 53% and 39% respectively (supplementary Figure 2A). Recurrence occurred in 123 of the 201 patients (61%) with a median delay of 24.3 [14.6-48] months. The median disease-free survival (DFS) was 16 months, with actuarial DFS survival rates at 1, 3 and 5 years of 60%, 37% and 28%, respectively (supplementary Figure 2B).

The treatments for recurrence were chemotherapy for 69 patients (62%), chemotherapy combined with radiofrequency ablation for 1 patient (1%), radiofrequency ablation for 3 patients (3%) and radiotherapy for 4 patients (4%).

Univariate analysis of factors affecting long term outcomes are provided in supplementary Table 1. Independent clinicopathological factors affecting OS and DFS are shown in Table 3. Particularly, Figures 1A and B highlights the influence of PBT on OS and DFS.

DISCUSSION

Few studies have specifically focused on the effect of post-operative morbidity on longer term outcomes following PD for DCC. The current study has identified that PBT had significantly impact on OS (HR=2.25 [1.31-3.85], *P*=0.003. PBT was also a significant independent factor for recurrence (HR=2.08 [1.24-3.50], *P*=0.005).

The finding that PBT adversely affects long term outcomes has been previously reported for patients with ampullary cancers (16–18), and in resected cholangiocarcinomas, whatever the employed surgery (19,20). One previous publication studied the effect of PBT on the outcomes for patients undergoing resection for cholangiocarcinoma, using a propensity score, which is a method to overcome some of the inherent many biases associated with retrospective studies (21). The authors reported that PBT did not impact on OS or DFS (*P*=0.974 and *P*=0.295, respectively). However, there was heterogeneity in the study population, including a mixture of patients with intrahepatic (23%), hilar (29%), and distal cholangiocarcinomas (48%). Therefore, several surgical techniques were performed and many patients were excluded in the propensity score-matched analysis (42%). Another study looked at the impact of PBT on the prognosis of patients who underwent resection for DCC but did not find a significant connection (*P*=0.0717) (22). The result was similar for patients with pancreatic cancer (*P*=0.610), but PBT remained an independent prognostic factor for patients with ampullary cancer (*P*=0.029).

An immunological mechanism for the adverse effect of transfusion has been suggested, but the immunosuppressive effect on patients with malignancy remains unclear. Such effects are probably due to the infusion of allogenic donor leukocytes, or their products, present in the

cellular blood products used for the transfusion (23). Immunomodulatory induced be allogenic blood tranfusion might increase the risk for postoperative infection.

Due to the complexity of this surgery and the frequent requirement of vascular reconstructions and adjacent organ resections, PBT are sometimes needed in PD (24). This surgery can lead to hemorrhage which are considered as a complication with relatively high mortality, particularly when these are late, needing a rapid diagnosis and treatment (5,6,25,26). However, it seems that 46% of transfusions in context of PD are not justified and induces others morbidities as higher rates of delayed gastric emptying (P=0.031), wound infection (P=0.031), pulmonary complications (P=0.032), urinary retention (P=0.032), and a greater incidence of any complication of grade II (P<0.001) or grade III severity ($P=0.01$) (27). Furthermore, a restrictive transfusion strategy doesn't seem to impact peri-operative morbidity, OS and DFS, and allows preservation of a limited resource, reduction in costs, and avoids exposing oncology patients to the unnecessary risks associated with a PBT (28). The American Society of Anesthesiologists has made recommendations concerning criteria of PBT based on abnormal heart rate, blood pressure, oxygen saturation, urine output, electrocardiographic changes, the degree of intraoperative blood loss, and decreasing hemoglobin or hematocrit values (29). However, few studies document such a standardized approach to PBT.

Within the current study, major complications were not a significant prognostic factor for OS or DFS. A recent study have analyzed surgical results and prognostic factors of DCC operated by PD (30). Postoperative morbidity was not a prognosis factor for univariate or multivariate analysis (P=0.3 and P=0.5 respectively). However, post-operative morbidity has been

identified as an independent predictor of worse long term outcomes in various cancers such as intrahepatic cholangiocarcinomas (31).

In our work, resections of adjacent organ and vascular resections were needed for 14 (6.5%) and 34 (15.7%) patients respectively, indicating advanced pathologies. Furthermore, adjacent organ resections were an independent risk factor of recurrence (HR=3.33 [1.52-7.32], *P*=0.002). Multivisceral resection combined with pancreatectomy for pancreatic cancer is regularly proposed to patients with adjacent organ invasion. This surgery, although feasible, is associated to a higher morbidity and mortality (32). Particularly, one study demonstrated that intra-operative blood transfusions in these complex procedures were significantly commoner than in standard pancreatectomies (*P*=0.019) or palliative bypass (*P*=0.019), and an independent factor influencing morbidity (*P*=0.05) and overall survival (*P*=0.05) (33).

Possible weaknesses of the present study should include the possibility of heterogeneity in peri-operative care given to patients due to the multicenter nature of the study. During the study period efforts to standardize and optimize management of PD across the organizations which should have helped reduce this as a potential source of bias. Finally, the retrospective character of the study induces inevitable bias and limited the interpretation of those results.

CONCLUSION

PBT following PD for DCC was found to be an independent prognosis factor influencing OS and DFS. Strategies to minimize the severity of the complications and restrict the need for PBT should be a point of focus in an effort to improve long term outcomes for these patients.

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TABLE AND FIGURE LEGENDS

Table 1. Patient characteristics.

Table 2. Postoperative outcomes.

Table 3. Multivariable analyses of clinicopathological factors that may influence overall and disease-free survivals.

Supplementary Table 1. Univariate analyses of clinicopathological factors that may influence overall and disease-free survivals.

Figure 1. Overall and disease-free survivals compared between patients who underwent PBT (black and dotted line) and those who did not (red line). (A) Overall survival *P*<0.001. (B) Disease-free survival, *P*=0.001.

Supplementary Figure 1. Flow chart.

Supplementary Figure 2. Overall and disease-free survivals of patients who underwent PD with curative intent for DCC (A) Overall survival. (B) Disease-free survival.

Table 1. Patient characteristics.

Variables	n=217	(%)
Preoperative		
Sex ratio (M:F)	136:81	-
Age (years, median [IQR])	66 [58-72]	-
ASA score		
1	42	(19)
2	137	(63)
3	38	(18)
Biliary dilatation	36	(64)
Pancreatic dilatation	16	(29)
Jaundice	190	(88)
Biliary stent	112	(52)
Neoadjuvant chemotherapy	39	(18)
Surgery		
Operative time (minutes, median [IQR])	340 [300-400]	-
Adjacent organ resection	14	(7)
Vascular resection	34	(16)
Wirsung drainage	135	(62)
Pathology		
R1 resections	32	(15)
T stage		
T1 and T2	67	(31)
T3 and T4	141	(65)
Lymph node invasion	116	(54)
Microvascular invasion	57	(26)
Perineural infiltration	129	(60)

IQR: Inter Quartile Range. ASA: American Society of Anesthesiologists.

Table 2. Postoperative outcomes.

Variables	n=217	(%)
Delayed gastric emptying		
None / Grade A	169	(78)
Grades B and C	32	(15)
Grade C	16	(7)
Pancreatic fistula		
None / Grade A	189	(87)
Grade B	14	(7)
Grade C	12	(6)
Biliary fistula	7	(3)
Postoperative haemorrhage		
No	168	(77)
Grade A	39	(18)
Grade B	6	(3)
Grade C	4	(2)
Peri-operative blood transfusion	75	(35)
Clavien grade ≥ 3B	51	(24)
Duration of hospital stay (days, median [IQR])	19 [11-19]	-
Readmission	24	(11)
Mortality at 30 days	13	(6)
Mortality at 90 days	16	(7)

IQR: Inter Quartile Range.

Table 3. Multivariate analyses of clinicopathological factors that may influence and disease-free survivals.

	Risk factors for overall survival		Risk factors for disease free survival	
Factors	**HR (95% CI)**	***P* value***	**HR (95% CI)**	***P* value[$]**
Adjacent organ resection	2.06 (0.90-4.70)	0.08	3.33 (1.52-7.32)	0.002
Microvascular invasion	1.56 (0.96-2.55)	0.06	1.79 (1.12-2.87)	0.014
R1 resections	2.52 (1.28-4.98)	0.007	-	-
≥ T3 stage	4.67 (2.43-8.96)	<0.001	3.21 (1.80-5.72)	<0.001
Positive lymph node	-	-	1.59 (0.96-2.64)	0.068
Peri-operative Transfusion	2.25 (1.31-3.85)	0.003	2.08 (1.24-3.50)	0.005
Adjuvant chemotherapy	-	-	0.61 (0.37-1.10)	0.057

BMI: Body Mass Index. ASA: American Society of Anesthesiologists. HR: Hazard Ratio. CI: Confidence Interval. *Final best Cox model with a Harrell's c-index = 0.73. [$]Final best Cox model with a Harrel's c-index = 0.71.

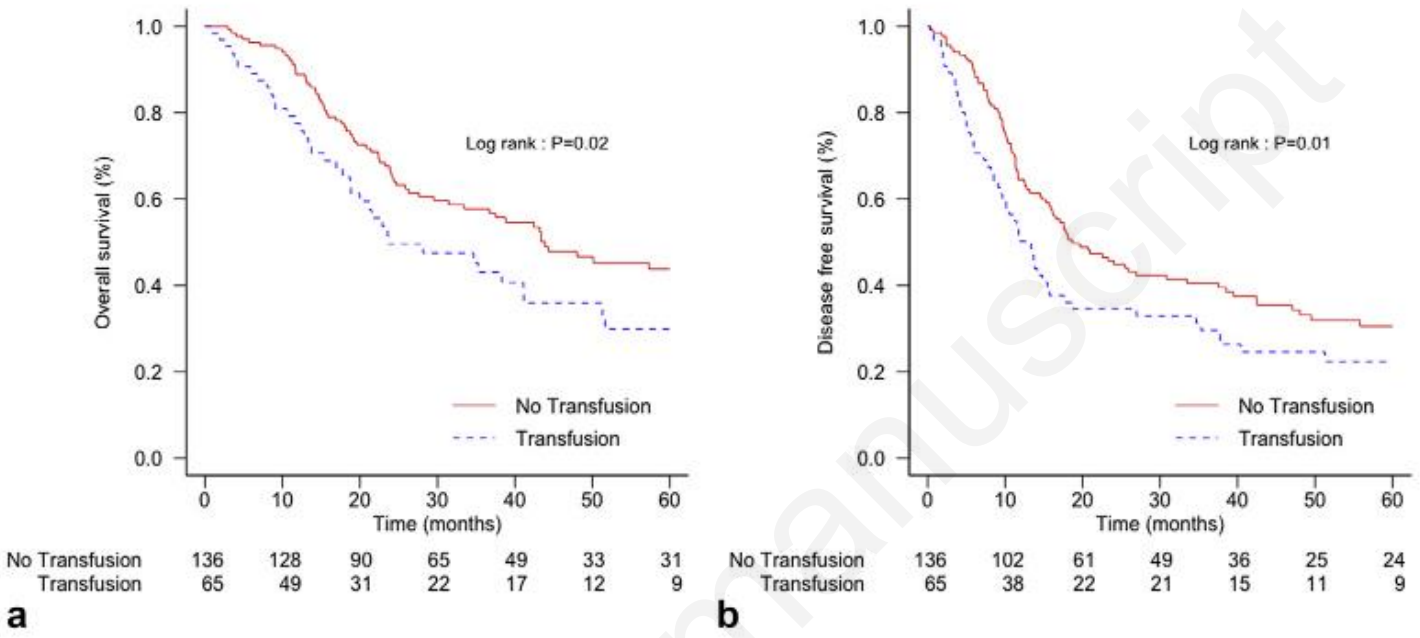

Figure 1 Overall and disease-free survivals compared between patients who underwent PBT (black and dotted line) and those who did not (red line). (a) Overall survival $P < 0.001$. (b) Disease-free survival, $P = 0.001$