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Pancreaticoduodenectomy for distal cholangiocarcinoma at a South African centre

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Background: Surgical resection of distal cholangiocarcinoma (dCCA) offers the only chance for cure and long-term survival. The current literature provides limited data regarding the surgical management and long-term outcomes of dCCA. This study aims to describe the presentation, management, and outcomes of dCCA at a large academic referral centre in South Africa.
Methods: A retrospective study was performed of all patients who underwent curative-intended surgery for dCCA at Groote Schuur Hospital from 2000 to 2020.
Results: Over 21 years, 25 patients underwent pancreaticoduodenectomy (PD) for dCCA. Most patients were male (68%), and the mean age was 56.8 years. Of the patients, 22 (84%) underwent preoperative biliary drainage (PBD). There were 29 recorded complications in 25 patients; postoperative pancreatic fistula (POPF) and surgical site infection (SSI) each occurred in 24% of the cohort. The mean hospital stay was 17.2 days without perioperative mortality. With none lost to follow-up, the 1, 3, 5, 10, and 20-year survival rates were 84%, 24%, 16%, 12%, and 4%, respectively. Only T3 status was associated with significantly lower overall survival (OS). Age, albumin levels, PBD, margin status (R0 vs. R1), and nodal status (N0 vs. N1/N2) did not influence OS.
Conclusions: This is the first study detailing the management and outcomes of dCCA from sub-Saharan Africa (SSA). Despite the complete resection of dCCA, the prognosis is poor, and the long-term survival rate in our study is equivalent to that reported in the literature. T3 disease is an important prognostic factor and is associated with poor OS. Surprisingly, nodal disease and margin status did not affect OS in the cohort of patients.
Keywords: distal cholangiocarcinoma, South Africa, sub-Saharan Africa, long-term outcomes, pancreaticoduodenectomy

Introduction

Constituting 13–23% of all extrahepatic biliary cancers, dCCA is defined as a tumour originating in the mucosa of the common bile duct below the confluence with the cystic duct and above the ampulla of Vater.[6,7] Despite the advent of multimodal treatment strategies, such as chemotherapy and, more recently, immunotherapy, surgical resection of dCCA offers patients the only chance for cure and long-term OS.[2-5,8-30] Surgical strategies for dCCA include pylorus-preserving pancreaticoduodenectomy (PPPD) and the Whipple procedure (PD).

Outcomes of curative surgery for dCCA are superior to those of pancreatic ductal carcinoma (PDAC), with reported disease-specific survival of 40 months and five-year disease-specific survival rates of 42%. In PDAC, the five-year disease-specific survival rate is less than 20%.[3,7,31,33] The resection margin and lymph node status are significant prognosticators of long-term disease-free survival (DFS) and OS.[3-5,34] The median survival of patients with R0 resection is 48 months, dramatically decreasing to nine months with R1 resection status. Moreover, patients with lymph node metastases will have lower median disease-specific survival (30 months) compared to lymph node-negative patients (60 months).[3,31,33] Given these mitigating factors, patient selection is paramount to ensure good long-term DFS and OS in dCCA.

There is a paucity of outcome data for cancer throughout SSA.[35] Studies detailing the management and outcomes of cholangiocarcinoma in SSA are limited, albeit a handful of publications from South Africa.[36-40] Only one study has reported on outcomes for dCCA in South Africa.[38] Consequently, this study aims to describe the presentation, management, and outcomes of dCCA at a large academic referral centre in South Africa.

Methods

In this retrospective single-centre cohort study, consecutive adult patients who underwent a PPPD or PD with curative intent for a dCCA between 2000 and 2020 were analysed. All the data were collected prospectively and recorded on a faculty-secure database. Documented information included sex, age, PBD, date of surgery, intensive care unit (ICU) length of stay, total hospital stay, in-hospital mortality, and 30-day and 90-day mortality. Postoperative complications were classified according to the Clavien-Dindo (CD) classification.[41]

PD with the removal of the distal part of the bile duct en bloc with the head of the pancreas, gallbladder, duodenum, and standard lymphadenectomy, according to the International Study Group for Pancreatic Surgery (ISGPS) recommendation was the standard procedure.[42] The reconstruction was performed with a pancreaticojejunostomy

(PJ), hepaticojejunostomy (HJ) and duodenojejunostomy (DJ).[43] All procedures were performed open.

All operative specimens were submitted for histopathological evaluation and were classified according to the American Joint Committee on Cancer (AJCC) classification for dCCA. R0 resection was defined as a margin ≥ 1 mm from the microscopic border of the tumour. In addition, pathological specimens were analysed for tumour size, lymphovascular invasion (LVI), perineural invasion (PNI), number of lymph nodes excised, and number of positive lymph nodes. Pathological evaluation included grading (low/moderate/high differentiation), T-stage, and N-stage.[44]

Specific procedure-related complications after PD included POPF, delayed gastric emptying (DGE), and postpancreatectomy haemorrhage (PPH), graded according to ISGPS definitions.[45-47]

Postoperative follow-up was performed every three months for two years and then every six months for up to five years. The follow-up included clinical examination, the level of carbohydrate antigen 19-9 (CA 19-9), and abdominal computed tomography every six months or in cases of elevated CA 19-9. The OS was measured as the period between the surgery date and the death date. Patients with a R0 resection received postoperative capecitabine, while patients with R1 resection/nodal disease were treated using a combination of cisplatin and gemcitabine.

Statistical analysis

Descriptive statistics, including median values with 95% confidence intervals (CI), were used to assess the distribution of continuous variables. Categorical variables were tabulated, and variations were assessed in proportions using Pearson's chi-square tests. The Kaplan-Meier method assessed OS differences among T-group patients (T1, T2, and T3). The logrank test was used to compare the survival curves amongst these groups. Additionally, a Mantel-Cox regression analysis was done to explore the impact of various factors on OS further. Assumptions underpinning all statistical tests performed, including the proportional hazard assumption for the Cox regression model, were assessed and confirmed to be met. The analyses used SPSS (Statistical Package for the Social Sciences) version 26 (IBM SPSS Armonk, New York, United States of America, 2019).

Results

There were 25 patients who had curative-intended surgery for dCCA. Baseline demographics and preoperative clinical and laboratory data are shown in Table I. Most patients were male (68%), and the mean age was 56.8 years. Jaundice and weight loss were the most frequent presenting symptoms in 92% and 56% of the cohort, respectively. Of the patients, 22 (84%) underwent PBD before PD; 21 underwent endoscopic retrograde pancreatography (ERCP), and one patient received a percutaneous transhepatic cholangiography (PTC) followed by a rendezvous procedure. A fully covered self-expandable metal stent (SEMS) was deployed in all cases of biliary drainage. After the PD, the pancreas was drained via a PJ in 22 (88%) patients and a pancreaticogastrostomy (PG) in three (12%) patients. A PPPD was the preferred procedure in 22/25 patients (Table I).

Postoperative complications and their management are depicted in Table II. There were 29 recorded complications in 25 patients. The two most common complications were POPF and SSI, each reported in six (24%) patients. The POPF were all ISGPS Grade B fistulae and resolved on conservative treatment. All patients who had SSI were treated with antibiotics and wound dressings. Three (12%) patients had ISGPS Grade B PPH, two required angioembolisation of the gastroduodenal artery (GDA), and one required a relook laparotomy and open ligation of the bleeding GDA stump. Four (16%) patients had ISGPS Grade A DGE after surgery; all were successfully managed with conservative management. All patients were discharged from hospital. The mean ICU and total hospital stay were 2.8 and 17.2 days, respectively. One patient was readmitted to the hospital 63 days after their PD and died of septic shock secondary to a complicated POPF.

Histopathological assessment of the resected specimen confirmed T3 and N1 disease in 44% and 80% of the patients, respectively. More specifically, five (25%) patients had N0 disease, and the remaining 20 (75%) had N1 disease. The tumours were well differentiated in six (24%) patients, moderately differentiated in 16 (64%), and poorly differentiated in two (8%). In one patient, the degree of tumour differentiation was not reported. The AJCC TNM staging was Stage IIB in 80% of the cohort. R0 resection

Table I: Demographic, clinical, preoperative, and operative data for 25 patients under curative-intended surgery for dCCA (data expressed as mean ± standard deviation [SD])

Gender, *n* (%)	
Males	17 (68)
Females	8 (32)
Age (years)	56.8 ± 9.8
Duration of symptoms (days)	27.6 ± 24.3
Presenting symptoms, *n* (%)	Jaundice, 23 (92) Pain, 11 (45.8) Weight loss, 14 (56) Pruritis, 10 (40)
Preoperative laboratory investigations	
• Haemoglobin (g/dl)	8.4 ± 6.1
• Leukocyte count (× 10^9/L)	6.9 ± 5.7
• Creatinine (µmol/L)	60.8 ± 48.7
• Carbohydrate antigen 19-9 (kU/L)	861.1 ± 4090.7
• Total bilirubin (µmol/L)	174.5 ± 178.3
Preoperative biliary drainage, *n* (%)	
• Endoscopic retrograde pancreatography and biliary stent	21 (84)
• Percutaneous transhepatic cholangiography and rendezvous procedure	1 (4)
Staging laparoscopy, *n* (%)	1 (4)
Operative data	
• Duration of surgery (min)	361 ± 58.6
• Blood loss (ml)	509.2 ± 422.2
• Blood transfusion (units)	0.2 ± 0.7
• Pancreatic anastomosis, *n* (%)	
◦ Pancreaticojejunostomy	22 (88)
◦ Pancreaticogastrostomy	3 (12)
• Resection technique, *n* (%)	
◦ Pylorus preserving pancreaticoduodenectomy	22 (88)
◦ Whipple procedure	3 (12)
Intensive care unit stay (days)	2.8 ± 3.9
Total hospital stay (days)	17.2 ± 13.7
Overall survival (days)	1361.0 ± 2033.7

Table II: Complications, management, and Clavien-Dindo classification grading

Complications *n* (%)		Management of complication	Clavien-Dindo classification grading
Postoperative pancreatic fistula (All Grade B)	6 (24)	Drainage	Grade I (6)
Postpancreatectomy haemorrhage (All Grade B)	3 (12)	Relook laparotomy and embolisation (1) Embolisation (1) Relook laparotomy (1)	Grade IIIb (3)
Surgical site infection	6 (24)	Wound dressings	Grade I (6)
Delayed gastric emptying (All Grade A)	4 (16)	Nasogastric drainage	Grade I (4)
Intrabdominal collection	2 (8)	Percutaneous drainage	Grade IIIa (2)
Anastomotic leak	2 (8)	Percutaneous drainage	Grade IIIa (2)
Chyle leak	1 (4)	Relook laparotomy	Grade IIIb (1)
Bile leak	1 (4)	Percutaneous drainage and total parenteral nutrition	Grade IIIa (1)
Pleural effusion	1 (4)	Percutaneous drainage	Grade IIIa (1)
Postoperative infections • *Clostridium difficile* colitis • Pneumonia • Septicaemia	 1 (4) 1 (4) 1 (4)	Antibiotics	Grade II (3)

Table III: American Joint Committee on Cancer TNM staging and pathology of 25 distal cholangiocarcinoma patients treated with curative-intended surgery

Pathological feature	TNM criteria	*n* (%)
Tumour size	T1	7 (28)
	T2	7 (28)
	T3	11 (44)
Regional lymph nodes	N0	5 (20)
	N1	20 (80)
Distant metastases	M0	25 (100)
Stage	IA	2 (8)
	IIA	3 (12)
	IIB	20 (80)
Resection margin	R0	14 (56)
	R1	11 (44)
Degree of differentiation	Well-differentiated	6 (24)
	Moderately differentiated	16 (64)
	Poorly differentiated	2 (8)
	Not reported	1 (4)

Table IV: Univariate Cox hazard ratio calculated for characteristics of patients in the study

	HR (95% CI)	*p*-value
Age (< 55 years)	0.76 (0.33–1.79)	0.54
> 55 years	1.31 (0.56–3.04)	0.54
R0	0.57 (0.25–1.29)	0.18
R1	1.77 (0.78–4.03)	0.18
T1	0.72 (0.30–1.77)	0.48
T2	0.53 (0.19–1.46)	0.22
T3	2.68 (1.06–6.79)	0.04
Albumin (< 35)	0.83 (0.36–1.96)	0.68
> 35	1.20 (0.51–2.82)	0.68
PBD (yes)	0.99 (0.40–2.44)	0.99
(no)	1.01 (0.41–2.48)	0.99
N0	0.81 (0.30–2.19)	0.68
N1	1.24 (0.46–3.34)	0.68

HR – hazard ratio, CI – confidence interval, PBD – preoperative biliary drainage

Table V: Characteristics of patients analysed in the study (*Mantel-Cox logrank test was performed)

	Median survival (IQR)	χ^2 *p*-value*
Age (< 55 years)	584 (418.75–853.50)	0.54
≥ 55 years	514 (421.50–951.75)	
R0	643 (414.00–898.00)	0.17
R1	433 (424.00–898.00)	
T1	709 (418.75–1059.25)	0.10
T2	490 (396.00–853.50)	
T3	514 (424.00–898.00)	
Albumin (< 35)	514 (424.00–898.00)	0.68
≥ 35	638 (411.00–1146.00)	
ERCP (yes)	638 (428.25–951.75)	0.98
(no)	490 (421.50–951.75)	

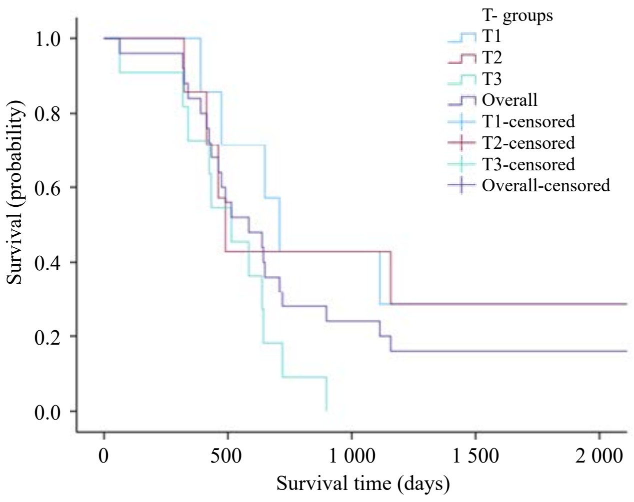
IQR – interquartile range, ERCP – endoscopic retrograde pancreatography

was done in 56%, and the remaining 44% had R1 resection (Table III).

No patients were lost to follow-up. The 1, 3, 5, 10, and 20-year survival rates were 84%, 24%, 16%, 12%, and 4%, respectively (Figure 1). A Mantel-Cox regression analysis showed that patients with T3 status had significantly higher hazard ratios (HR) and lower OS compared to those with T1 and T2 disease (HR = 2.68 [1.06–6.79], $p = 0.04$). Age, albumin levels, PBD, margin status (R0 vs. R1), and nodal status (N0 vs. N1/N2) did not influence OS (Tables IV and V).

Discussion

Studies reporting on the management and outcomes of dCCA are uncommon due to the rarity of this tumour. The present study focuses on 25 consecutive patients with dCCA who underwent surgery with curative intent at a large academic centre in South Africa over 21 years. To the best of our knowledge, this is the first study of its kind from SSA and one of few studies to report on the long-term outcomes of PD for dCCA in the global literature.[14-18,21,23,24,26-29,48]



***n* at risk**					
T1	7	5	3	2	2
T2	7	3	3	2	2
T3	11	6	0	0	0
Overall	25	14	6	4	4

Figure 1: Kaplan-Meier curves illustrating the relationship between T-groups and overall survival of patients

Most patients were males in their mid-50s who presented with jaundice and weight loss, findings corroborated by previously published studies.[3,17,25-28,33,38,39,48-52] With a mean total bilirubin level of 174.5 µmol/L at presentation, 88% (22 patients) of the cohort underwent PBD followed by the deployment of a fully covered SEMS. PBD remains controversial and has been associated with increased perioperative morbidity and bleeding in periampullary cancers.[53-55] At our institution, PBD is liberally used to treat cholangitis and assist in the prehabilitation of patients with malignant obstructive jaundice. In this study, PBD was not associated with perioperative morbidity and did not influence OS. Patients with PBD had a median survival of 638 days, while those without drainage had a median survival of 490 days (HR = 0.99 [0.40–2.44], p = 0.99). This observation likely results from the study's small sample size.

In 88% of the patients, the operative procedure was a PPPD. The incidence of DGE was 16% (all Grade A) in this study and is comparable to data in the international literature.[56-60] As advocated by many groups, an antecolic reconstruction was used to mitigate DGE after PPPD.[56,58,59,61,62] To encourage early enteral feeding as part of an enhanced recovery after surgery (ERAS) programme, a nasojejunal tube is passed down in all patients undergoing PPPD at our institution and semi-elemental feeds are initiated on day 0 after surgery.[63,64] A subgroup analysis to determine whether the type of resection (PPPD vs. Whipple) and pancreatic anastomosis (PJ vs. PG) were associated with DGE was not possible, given this study's small cohort size.

Despite the availability of new chemotherapeutic agents and advances in surgical care, DFS and OS in patients undergoing PD for dCCA have not drastically improved over the last two decades.[1-5,8,9,12,15-29,32-34,39,42,48-52] Long-term follow-up was available in all 25 patients; at three, five, and ten years post-surgery, only 24%, 16%, and 12% were alive, respectively. Identifying prognosticators of OS for dCCA is a critical step in achieving optimal patient selection and improving long-term survival after curative surgery. In a systematic review of 3 258 patients from 39 studies, Zhou et al.[4] identified vital prognostic factors of OS in patients undergoing curative surgery for dCCA. R1 resection status, lymph node metastasis, PNI, vascular invasion, pancreatic invasion, and T3 lesions were associated with shorter OS. Similarly, in our study, T3 lesions were associated with lower OS (HR = 2.68 [1.06–6.79], p = 0.04). Interestingly, in keeping with the global epidemiology of dCCA, 25/39 publications in this meta-analysis originated from Asia, but there were no studies from Africa.[4]

Whilst it is widely accepted that lymph node dissection is an important component of staging, positive lymph node status was not associated with poorer OS in our analysis (HR = 1.24 [0.46–3.34], p = 0.68) despite 80% of the patients having N1 disease. Likewise, in a study of 118 patients with dCCA, Noji et al.[51] showed that extracapsular lymph node involvement did not impact OS and DFS. An analysis of 56 dCCA patients treated with curative intent by Courtin-Tanguy et al.[30] revealed that 50% had positive lymph node status; again, these patients did not have inferior DFS and OS.

A positive surgical margin is a strong predictor of early recurrence and poor survival in dCCA.[65-67] The rates of tumour-free margin at the bile duct stump vary in the literature. In the University of California-San Francisco group experience, only 22% of patients resected for extrahepatic cholangiocarcinoma had microscopically negative margins.[68] In a Japanese study, Ebata et al.[23] reported microscopically positive tumour margins in 31.6% of their patients. At a high-volume Korean centre, Jang et al.[69] showed that in 15.9% of resections, the bile duct margin was microscopically positive. In our experience, 44% of the patients had positive microscopic margins on histology. Interestingly, in our cohort, an R1 status did not result in inferior OS (HR = 1.77 [0.78–4.03], p = 0.18) compared to R0 resections. Two large Japanese studies have shown that this paradoxical survival rate results from positive resection margins comprised of two entities: residual invasive carcinoma at the resection margin and carcinoma in situ at the margin.[19,70] Sasaki et al.[19] investigated the significance of ductal margin status in 108 patients undergoing resection for extrahepatic cholangiocarcinoma; 18% had a positive resection margin.

Whilst a positive margin was associated with early recurrence and lower survival, a subgroup analysis showed that patients with residual carcinoma in situ did not have inferior survival despite the positive margin status.[19] These results were also replicated by Wakai et al.,[70] who showed that patients with residual carcinoma in situ at the ductal stumps had better prognosis than those with invasive carcinoma. Surgeons need to be aware of these entities, given that different histological findings significantly impact the long-term survival of dCCA patients.

Although this study included only 25 patients, follow-up was complete in the cohort. There are limited long-term outcome data for patients undergoing curative-intended surgery for dCCA. In a systematic review and meta-analysis of prognostic factors for survival after surgical resection for dCCA, Zhou et al.[4] examined 39 studies, of which only 16 reported on perioperative mortality, median survival, and one-, three-, and five-year survival rates.

In our study, only one patient died within 90 days of surgery. The mean OS was 1 361.0 days (SD ± 2 033.7); a 20-year follow-up was achieved in this cohort. The one-, three-, and five-year survival rates were 84%, 24%, and 16%, respectively, and compared well with international results.[4] A unique contribution from this cohort is the availability of 10- and 20-year survival data, which was 12% and 4%, respectively.

Conclusion

This first study, which detailed the management and outcomes of dCCA from SSA, showed no in-hospital mortality after PPPD resection. Most patients had endoscopic stenting to relieve jaundice before surgery. Despite the complete resection of dCCA, the prognosis is poor, and the long-term survival rate in our study is equivalent to that reported in the literature. Surprisingly, nodal disease and margin status did not affect OS. T3 disease is an important prognostic factor and is associated with poor OS.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This study was approved by the University of Cape Town Human Research Ethics Committee (HREC reference number: 247/2022).

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