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ORIGINAL RESEARCH

Prognostic Factors and the Role of Adjuvant Treatment in Periampullary Carcinoma: a Single-Centre Experience of 95 Patients

Saphalta Baghmar[1] · Nikhil Agrawal[2] · Guresh Kumar[3] · Chhagan Bihari[4] · Yashwant Patidar[5] · Senthil Kumar[2] · Tushar Kanti Chattopadhyay[2] · Dipanjan Panda[6] · Asit Arora[2] · Viniyendra Pamecha[2]

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Abstract

Purpose The effect of adjuvant treatment on those undergoing pancreaticoduodenectomy (PD) for periampullary carcinomas (PAC) is not well studied. Most studies employed chemoradiation as the adjuvant modality. We aimed to analyse clinicopathological differences between types of PACs, the prognostic factors and the role of adjuvant therapy (chemotherapy in the majority).

Methods Patients with PAC who underwent PD from Jan 2011 to Dec 2015 were retrospectively analysed.

Results Ninety-five patients with PAC underwent PD in the study period. Ampullary carcinoma (AC) was the most common. Pancreatic carcinomas (PC) were larger. AC had lower T stage, perineural invasion (PNI) and R1 resections. Median overall survival (OS) was 32.7 months. On multivariate analysis, lymph node ratio (LNR) ≥ 0.2 and advanced T stage adversely affected the OS. Fifty-seven (66.3%) patients received adjuvant treatment, of which 50 had chemotherapy alone. Adjuvant treatment resulted in better OS in patients with T stage ≥ 3, lymph node involvement, LNR ≥ 0.2, lymphovascular invasion, PNI, tumour size > 2 cm, higher grade and distal cholangiocarcinoma.

Conclusion In patients of PAC undergoing PD, AC had favourable clinicopathological profile. LNR ≥ 0.2 and advanced T stage adversely affected OS. Adjuvant treatment resulted in significantly better OS in patients with high-risk features.

Keywords Periampullary carcinoma · Prognostic factors · Lymphnode ratio · Adjuvant treatment

✉ Nikhil Agrawal
drnkhl@gmail.com

Saphalta Baghmar
drbsaphalta@gmail.com

Guresh Kumar
chibbegk@gmail.com

Chhagan Bihari
drcbsharma@gmail.com

Yashwant Patidar
dryashwantpatidar@gmail.com

Senthil Kumar
sanskrity@hotmail.com

Tushar Kanti Chattopadhyay
tkc46@hotmail.com

Dipanjan Panda
dipanjan.panda@gmail.com

Asit Arora
drasitarora@yahoo.com

Viniyendra Pamecha
viniyendra@yahoo.co.uk

[1] Department of Medical Oncology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi 110070, India

[2] Department of Hepatopancreatobiliary Surgery, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi 110070, India

[3] Department of Biostatistics, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi 110070, India

[4] Department of Pathology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi 110070, India

[5] Department of Radiology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi 110070, India

[6] Department of Medical Oncology, Indraprasth Apollo Hospital, New Delhi 110076, India

Introduction

Periampullary carcinomas (PAC) account for 0.5–2% of all gastrointestinal malignancies. They are defined as tumours arising within 2 cm of the major papilla in the duodenum and include four different types of malignancies, namely those originating from (a) the ampulla of Vater (20–30%), (b) the intrapancreatic distal bile duct (10%), (c) the head and uncinate process of the pancreas, which is most common (50–60%) and (d) the duodenum, which is the least common, constituting < 10% of all the resected specimens [1].

Pancreaticoduodenectomy (PD) is the standard treatment for those who are resectable at presentation. The prognostic factors following resection, in the literature are: the site of origin, stage, tumour size, pre-operative biliary drainage (PBD), R0 resection, absence of surgical complications, lymph node (LN) status, lymph node ratio (LNR), perineural invasion (PNI), lymphovascular invasion (LVI), histopathological phenotype and grade of differentiation [1–10].

Despite the high rate of potentially curative resections in contemporary series, more than half of the patients will have recurrent disease, highlighting the need for effective adjuvant therapy. Randomised clinical trials and retrospective studies have evaluated the role of adjuvant chemotherapy or chemoradiotherapy (CTRT) versus observation with varied results.

We have analysed the clinicopathological differences between types of PACs, prognostic factors and benefit of adjuvant treatment in patients undergoing PD for PAC at our institute, a tertiary care centre dedicated to hepatopancreatobiliary diseases.

Materials and Methods

Inclusion Criteria and Data Collection

All patients who underwent PD for PAC between January 2011 and December 2015 at the Institute of Liver and Biliary Sciences, New Delhi were identified and data was extracted from a database. PAC was defined as adenocarcinoma originating in the epithelia of the ampulla of Vater (ampullary carcinoma [AC]), distal bile duct (distal cholangiocarcinoma [DCC]), the proximal–mid-duodenum (duodenal carcinoma [DC]) or the head of pancreas (pancreatic carcinoma [PC]). Intraductal papillary mucinous neoplasms and neuroendocrine tumours were excluded.

Patient demographics, tumour staging and pathological data, surgical treatment-related variables, adjuvant treatment and follow-up data were retrieved. Demographic factors evaluated included age, gender and co-morbid illnesses. Work-up included complete blood counts, liver function test, renal function test, tumour marker, chest roentgenogram and contrast-enhanced computed tomography scan of abdomen. PBD was done if bilirubin was > 15 mg% or clinically indicated. Some of the patients were referred after PBD. Surgical procedures included pylorus preserving pancreaticoduodenectomy and classical Whipple. The PD specimens were examined and staged as per the College of American Pathologists and American Joint Committee on Cancer, 2010 protocol [11, 12]. The location of the tumour was determined on gross and microscopic examination of the specimens. Margins assessed included the pancreatic neck resection margin, biliary margin, bowel margins (proximal and distal) and uncinated/superior mesenteric artery margin. R1 resection was defined as distance of tumour from the resection margin of < 1 mm.

Maximal tumour size was determined and defined as the maximum diameter of tumour at pathological examination. Pathological factors that were evaluated included site of tumour, T and N stage, lymph node ratio, margin status, size of tumour and tumours ≥ 2 cm, LVI, PNI, histopathological phenotype (pancreatobiliary, PB; expressing CK7 and MUC1 vs intestinal; expressing CK20, MUC2 and CDX2) [14, 15] and histological differentiation (well, moderate and poor).

LNR was defined as number of nodes involved by the tumour divided by the number of nodes examined. A cut-off value of ≥ 0.2 was assigned based on previous study [16]. LVI and PNI were defined as microscopic tumour invasion of the microvascular or neural element of the surrounding normal tissue, respectively.

Adjuvant treatment was administered to 57 patients and it was either chemotherapy (gemcitabine 1 g/m^2 D1, 8 and 15 q 4 weekly or gemcitabine 900 mg/m^2 + cisplatin 25 mg/m^2 D1 and 8 q 3 weekly or capecitabine 1 g/m^2 D1 to D14 + oxaliplatin 130 mg/m^2 on D1 [6–8 cycles]) or CTRT (52 Gy/25 fractions to the tumour bed with capecitabine 625 mg/m^2 twice daily on radiotherapy days). It was preferably started within 4–6 weeks of surgery. The reasons for not receiving adjuvant treatment included (a) patient preference, (b) T1 and T2 tumours without node positivity, LVI and PNI, (c) poor general condition and (d) post-operative complications prolonging hospital course.

Follow-up visits were done every 3 months during the first 2 years, every 6 months for the next 3 years and once a year later. Investigations in the follow-up visits included routine laboratory tests, tumour marker, chest roentgenogram and abdominal ultrasound or contrast-enhanced computed tomography.

Overall survival (OS) was measured from date of resection to date of censor or death from any cause. Progression free survival (PFS) was measured from date of resection to date of recurrence.

Peri-operative mortality was defined as death within 60 days after resection and such patients were excluded from long-term survival analysis.

The study was approved by the institutional internal review board.

Statistical Analysis

SPSS Version 22 (IBM Corp: Armonk NY, USA) was used for analysis. Results are expressed as either median (range) or mean ± SD. Comparisons between categorical variables were analysed using the χ^2 test. Continuous variables were expressed as medians and ranges and compared using the Mann–Whitney test. Variables influencing overall and disease-free survival rates were analysed using the univariate and multivariate Cox regression analysis. The Kaplan–Meier method with log-rank test was used for survival analysis. The results are reported as a hazard ratio (HR) with 95% confidence intervals. A $p < 0.05$ was considered statistically significant.

Results

In the study period, 115 patients underwent PD of which 95 patients had PACs. The cohort included 43 patients of AC (45.3%), 25 of DCC (26.3%), 15 of PC (15.8%) and 9 of DC (9.5%). Site of origin could not be ascertained in three patients.

The median age of the entire cohort was 57.5 years (range 29–76). Sixty five (68.5%) were men. Median duration of symptoms was 1.8 months. Patients presented with obstructive jaundice in 77.4%, weight loss in 66.7%, abdominal pain in 36.6%, fever in 27% and abdominal mass in 3.2%. The clinical and pathological profile of the patients is summarised in Table 1.

Comparisons in Pathological Data

The overall median tumour size was 2.5 cm (range 0.7–7) (Table 1) and it was similar for AC, DC and DCC. The PCs were larger (median tumour size and those with tumours ≥ 2 cm) than other PACs ($p < 0.001$). The T3 and T4 tumours were significantly lower in patients of AC ($p < 0.001$).

PNI was lower in AC compared to DCC ($p = 0.003$). PB histology was significantly lower in DC and AC compared to DCC ($p = 0.01$) and PC ($p = 0.002$). Histological differentiation between PB and intestinal type could not be ascertained in eight cases.

The overall rate of R1 resection was 14%. R1 resection rate was higher in PC and DCC compared to AC. The median number of retrieved LNs was 15 (range 1–46) and positive LNs was 1 (range 1–21).

Comparisons in Survival

The median follow up was 17.4 months (range 0.33–61.3). Recurrence was seen in 43 patients (45%) of which 7 had only locoregional recurrence. The liver (70%) was the most common site of distant recurrence followed by the lung (14%), lymph nodes (12%) and peritoneum (7%). Thirty-nine (41%) patients expired, out of which 4 died during treatment (2 post-operatively and 2 due to chemotoxicity).

The median PFS of the whole cohort was 30.4 months (range 2.21–58.5). In univariate analysis, LN positivity, LNR ≥ 0.2, LVI and PC were predictors of poor PFS. In a Cox proportional hazards multivariate regression model,

Table 1 Clinical and pathological profile

Variables	Ampullary $n = 43$	Bile duct $n = 25$	Pancreas $n = 15$	Duodenum $n = 9$	p value
Age, in years; median (range)	55 (34–71)	62 (29–71)	57 (49–73)	54 (35–67)	0.18
Male gender; *n* (%)	27 (62.8)	20 (80)	7 (46.7)	8 (89)	0.07
PBD; *n* (%)	8 (18.6)	11 (44)	4 (26.7)	2 (22.2)	0.15
T3 and T4 tumours; *n* (%)	15 (35)	21(84)	11 (73.3)	7 (77.7)	0.001
Tumour size, in cm; median (range)	2 (0.8–7)	2.25 (1.3–4)	4 (1–6)	2.5 (0.7–5)	0.001
Tumour size > 2 cm; *n* (%)	18 (42)	13 (52)	14 (93.3)	4 (36)	0.005
Node positive; *n* (%)	25 (58)	18 (72)	9 (60)	4 (36)	0.7
LNR; median (range)	0.08 (0–0.66)	0.12 (0–0.6)	0.05 (0–0.7)	0.0 (0–0.23)	0.23
PNI; *n* (%)	22 (51.5)	21 (87.5)	12 (80)	6 (66.7)	0.014
LVI; *n* (%)	19 (44.5)	15 (62.5)	8 (53.3)	3 (33.3)	0.37
R1 resection; *n* (%)	1 (2.3)	6 (25)	6 (40)	1 (11)	0.002
PB histology; *n* (%)	22 (55.5)	14 (63.3)	12 (80)	1 (11)	0.017
Grade ≥ 2; *n* (%)	29 (67.4)	18 (72)	11 (73.3)	6 (66.7)	0.9

LNR lymph node ratio, *PNI* perineural invasion, *LVI* lymphovascular invasion, *PB* pancreatobiliary, *PBD* preoperative biliary drainage

LNR ≥ 0.2 (hazard ratio [HR] = 3.2, 95% confidence interval [CI] 1.6–6.2; $p = 0.001$) and LVI (HR = 3.2, 95% CI 1.5–6.5; $p = 0.001$) significantly affected PFS (Table 2).

The median and 5-year OS for the entire cohort was 32.7 months (range 4.6–60) and 23.4%, respectively. Survival varied among the various PAC types. DCC was associated with the worst median OS (15.6 months), followed by PC (24.9 months) and DC (32.3 months); not reached for AC (Fig. 1). Similarly, the estimated 5-year survival was lowest for DCC (21%) followed by PC (33%), DC (40%) and AC (66%).

Patients with PC and DCC, T3 and T4 tumours, node positivity, LNR ≥ 0.2, PBD and tumour size ≥ 2 cm (70.5%) had significantly poor OS on univariate analysis (Table 3). On multivariate analysis, LNR ≥ 0.2 (HR = 2.2, 95% CI 0.98–5.3; $p < 0.056$) and advanced T stage (HR = 3.6, 95% CI 1.2–10.7; $p = 0.01$) predicted poor OS. Date of censoring was 30/11/2016.

Age, gender, comorbid illnesses, margin status, lymphocyte neutrophil ratio, serum albumin <3.5 mg/dl, baseline CA19.9 levels, weight loss and presence of obstructive jaundice at the time of presentation did not affect OS.

Table 2 Tumour characteristics and predictors for progression-free survival

Variables	Frequency (%)	HR (95% CI)	*p* value
T stage			
T1	7 (7.4)	T3/4 vs T1/2	
T2	31(32.6)		
T3	53(55.8)	2.3 (1.17–4.6)	
T4	4 (4.2)		0.018
Node positive	59 (62.2)	3.5 (1.6–7.6)	0.002
LNR			
< 0.2	63 (66.3)	1	
≥ 0.2	32 (33.6)	3.7 (1.9–7.1)	0.001
Tumour size			
≤ 2 cm	43 (45.2)	1	
> 2 cm	52 (54.7)	1.2 (0.98–1.5)	0.076
Site			
Ampullary	43 (45.3)	1	
Bile duct	25 (26.3)	1.9(0.49–3.5)	0.087
Duodenum	9 (9.5)	1.06(0.24–3.3)	0.91
Pancreas	15 (15.8)	2.4(1.4–5.5)	0.037
Site not identified	3 (3.2)	–	–
Grade			
1	29 (30.9)	1 vs 2/3	
2	63 (67)		
3	3 (3.1)	1.7 (0.7–3.8)	0.16
Histology			
Intestinal	37 (38.9)		
PB	50 (52.6)	1.15(0.6–2.2)	0.63
Not identified	8 (8.4)	–	–
R1 resection	14 (15)	1.3 (0.55–3.1)	0.51
PNI	63 (67)	1.2 (0.6–2.3)	0.56
LVI	47 (50)	3.2 (1.6–6.2)	0.001
PBD	26 (27.3)	1.4 (0.7–2.9)	0.3

LNR lymph node ratio, *PNI* perineural invasion, *LVI* lymphovascular invasion, *PB* pancreatobiliary, *PBD* pre-operative biliary drainage

Adjuvant Treatment

Fifty-seven (66.3%) patients received adjuvant treatment (50-chemotherapy; 7-CTRT). The details of adjuvant treatment in eight patients was not clearly known, as they followed up at other hospitals, so they were not included. Thirty-four (59.6%) patients received single agent gemcitabine, 11 (19%) gemcitabine with cisplatin/oxaliplatin and 5 (8.5%) received capecitabine, oxaliplatin combination. Median number of cycles was 5 (range 3–8).

The chemotoxicities were mainly grade 1 and 2. Grade 3 or more toxicities included haematological (neutropenia 8%, anaemia 2%, thrombocytopenia 3%) and non-haematological (alopecia 1%, fatigue 10%, nausea/vomiting 2%, febrile neutropenia 4%, impaired renal function 2%, impaired liver function 4%, deep venous thrombosis 2%). Two patients died during chemotherapy; one with capecitabine-induced diarrhoea, who did not report to the hospital and another patient died due to pancreatitis which developed during last cycle of single agent gemcitabine.

The patients with T stage ≥ 3, LN involvement, LNR ≥ 0.2, LVI, PNI, tumour size > 2 cm and PC had significantly better PFS with adjuvant treatment. Adjuvant treatment resulted in significantly better OS in patients with T stage ≥ 3, lymph node involvement, LNR ≥ 0.2, LVI, PNI, tumour size > 2 cm, higher grade, PB histology and DCC (Table 4).

Thirty-eight patients did not receive adjuvant therapy. Reasons were (a) T1/2 tumours, node negative and without LVI and PNI, (b) refused adjuvant treatment, (c) had post-operative complications and prolonged hospital course or (d) were frail to take adjuvant treatment.

Prognostic Factors in Patients Who Received Adjuvant Treatment

On analysis of the prognostic factors among 57 patients, who had received adjuvant treatment, LNR ≥ 0.2 (HR 2.75, 95% CI 1.2 6.4; *p* 0.018) and LVI (HR 3.05, 95% CI 1.25 7.4; *p* 0.014) predicted poor PFS. LVI (HR 3.14, 95% CI 1.2 8.3; *p* 0.021), PBD (HR 2.6, 95% CI 1.01 6.5; *p* 0.047), LNR ≥ 0.2

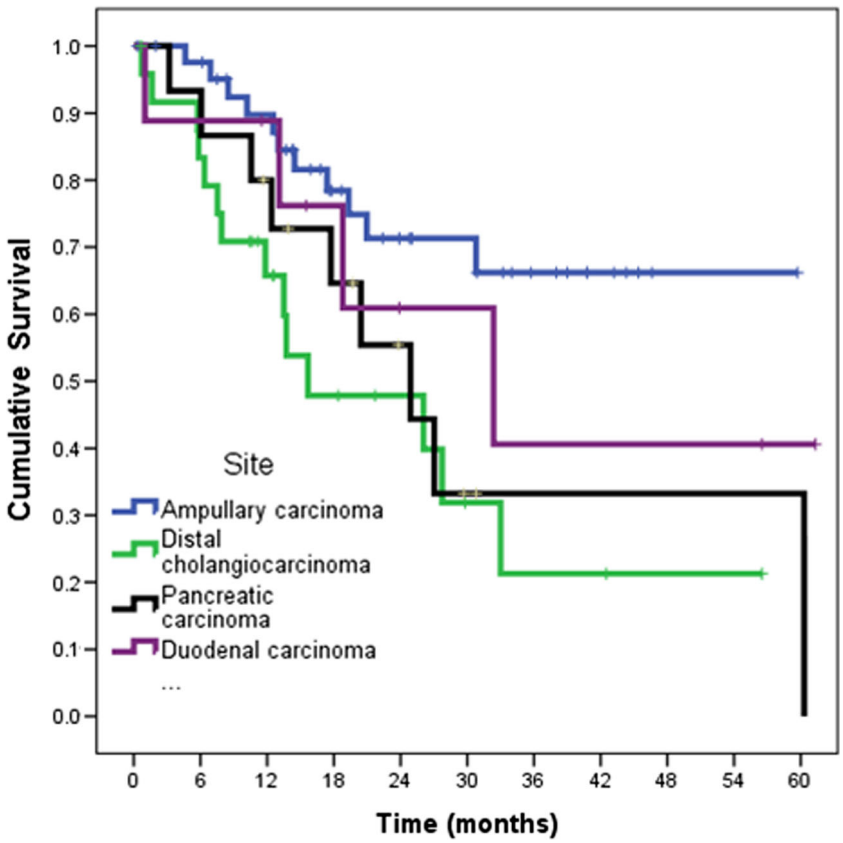

Fig. 1 Median overall survival of periampullary carcinomas

(HR 3.4, 95% CI 1.4 8.5; p 0.008) and T stage ≥ 3 (HR 3.5, 95% CI 1.18 10.8; p 0.02) significantly affected OS.

Discussion

In our study, patients with AC had lower T stage and R1 resection as compared to DCC and PC. PNI was also less prevalent in AC as compared to DCC. Patients with PC presented with larger tumours as compared to AC and DCC. They had similar node positivity rate, LNR, LVI and tumour grade. PB histology was less common in DC and it was also less common in AC when compared to PC ($p = 0.09$). Berberate et al. [1] also found lower T stage in AC compared to PC. Larger tumour size and R1 resection was significantly more in PC, which has also been shown by Kim et al. [3]. Other studies have also shown PC to be larger and associated with higher R1 resection rate compared to non-pancreatic periampullary carcinoma (NPPAC) [13, 14].

The AC cohort in our study had a higher proportion of patients with PB histology (55.5%) compared to previous studies, which had suggested that histology and genetic association of AC is closer to intestinal than to PB cancers [15, 16]. However, a recent study by Williams JL et al. [14] showed PB histology to be present in 48.2% of their AC patients. Twenty percent of PC and 36.7% of DCC in our study had intestinal differentiation. This variation in histological types of presentation may arise due to a common embryologic origin, error in judging the origin of tumour or difficulties in reliably differentiating them by immunohistochemical staining pattern.

The median and 5-year OS for the entire cohort was 32.7 months (range 4.6–60) and 23.4%, respectively. In two large studies which looked at survival of the entire PAC cohort, the median OS was 22 and 34.3 months [13, 14].

PACs are associated with significantly different long-term survival rates. In our study, DCC was associated with the worst survival and AC with best (Fig. 1). In most studies, it was shown that the AC and DC have the best overall survival, intermediate for patients with DCC and least for patients with PC [1, 13, 17]. While in some, PC and DCC both have poor long-term survival (Table 5) [2, 18]. In our study, both PC and DCC had poor outcome. Clinical and pathological factors were also comparable between these two, except that the PCs were larger. The survival of PC patients in our series is higher than that reported in the literature. One possible explanation to this can be the small number of patients with PC in our study.

The difference in outcome of these tumours is interesting in view of the fact that these cancers originate in tissues that are so close and have almost identical lymphatic and venous drainage and are often difficult to differentiate on standard histopathological examination. The difference in ‘biological

Table 3 Tumour characteristics and predictors for overall survival

Variables	Frequency (%)	HR (95% CI)	*p* value
T stage			
T1	7 (7.4)	(T3/4 vs T1/2)	
T2	31(32.6)		
T3	53 (55.8)	3.3 (1.5–7.2)	0.003
T4	4 (4.2)		
Node positive	59 (62)	2.4 (1.17–5.1)	0.017
LNR			
< 0.2	63 (66.3)	1	
≥ 0.2	32 (33.6)	3.5 (1.8–6.8)	0.000
Tumour size			
≤ 2 cm	43 (45.2)		
> 2 cm	52 (54.7)	1.3 (1.07–1.67)	0.007
Grade			
1	29 (30.9)		
2	63 (67)	(1 vs 2/3)	
3	2 (2.1)	1.55 (0.7–3.3)	0.25
Histology			
Intestinal	37 (38.9)		
PB	50 (52.6)	0.76 (0.39–1.5)	0.43
Not identified	8 (8.4)	–	
R1 resection	14 (15)	1.9 (0.89–4.3)	0.09
PNI	63 (67)	1.9 (0.9–4.0)	0.06
LVI	47 (50)	2.5 (2.5–4.9)	0.007
PBD	26 (27.3)	2.3 (1.16–4.3)	0.016
Site			
Ampulla	43 (45.3)	1	
Bile duct	25 (26.3)	3.2 (1.4–7.1	0.004
Duodenum	9 (9.5)	1.6 (0.49–5)	0.43
Pancreas	15(15.8)	2.4 (1.01–6.09)	0.047
Site not identified	3 (3.2)		

LNR lymph node ratio, *PNI* perineural invasion, *LVI* lymphovascular invasion, *PB* pancreatobiliary, *PBD* pre-operative biliary drainage

behaviour' can be the plausible explanation to this, as stated by Ehehalt et al. [19].

Prognostic factors adversely affecting survival, reported in literature are: origin of tumour, T3 and T4 tumours, larger tumours, positive LN, LNR ≥ 0.2, PNI, LVI, positive margin, PB histology, higher grade, PBD, CRP, CA 19.9, postoperative complications and vascular resection (Table 5).

In our study, LNR ≥ 0.2 adversely affected both PFS and OS, while LVI and advanced T stage adversely impacted only the PFS and OS, respectively. A large study of 2564 patients showed tumour type, vein resection rate, margin status and nodal status to be associated with worse survival [13]. The R1 resection rate in their study was 21%, while, it was 15% in our study, which could have precluded meaningful analysis. The studies that evaluated prognostic factors in ACs (which constituted the majority of our patients) did not find R1 resections adversely affecting survival [9, 20].

The PB differentiation predicts poor prognosis in PACs [14, 21, 22]. In our study, it did not affect survival. ACs in our study had higher number of tumours with PB differentiation compared to that usually reported in the literature while 20% of PCs and 36.7% of DCCs had intestinal differentiation as well. We also could not ascertain the differentiation in eight patients.

In a study by Williams et al. [14], 28% of the patients had grade III tumour, which did worse. While in our study, only 4% of the patients had grade III tumour. We analysed grade II and III together and it did not affect survival.

LN positivity has been shown to be a poor prognostic factor in many of the studies [13, 14, 20, 23, 24]. LN positivity was present in 62.2% of the patients; however, it was not found to be a prognostic factor. LNR ≥ 0.2 was the only factor which independently affected PFS, OS and improved survival with adjuvant treatment.

The 5-year survival has not improved significantly over the past decade and rarely exceeds 25%, with better results for AC and DC and worse outcomes for PC and DCC [35]. Adjuvant treatment is often administered to these patients in an attempt to improve survival. There is still no consensus regarding the indication and regimen for adjuvant therapy in NPPAC [26–28]. In clinical practice, treatment regimens for AC, DC and DCC are usually extrapolated from PC.

Limited data suggests that patients with node-positive and margin-positive AC benefit from adjuvant therapy [36–40]. The Johns Hopkins Hospital-Mayo clinic collaborative study for AC showed a significant survival benefit for patients with positive LNs treated with adjuvant CTRT [37]. But many of the retrospective studies including a meta-analysis and randomised trial by EORTC did not find benefit of adjuvant CTRT in PACs [41–45]. The systematic review included 14 studies but due to significant heterogeneity in the treatment regimens used in the studies, with variation in the number of chemotherapy cycles and use of radiotherapy, it was not possible to analyse the value of the various treatment regimens employed [45]. The limitations of EORTC study were: only 70% of the patients assigned to post-operative CTRT actually received it; it included a significant number of patients with T1–2 and N0; and an outdated split-course radiation technique was employed [44].

In ESPAC-3 trial, adjuvant chemotherapy had survival benefit in PAC patients when adjusted for independent prognostic variables of age, bile duct cancer, poor tumour differentiation and positive lymph nodes [38].

In our study, adjuvant therapy improved OS in patients having T stage ≥ 3, lymph node involvement, LNR ≥ 0.2, LVI, PNI, tumour size > 2 cm, moderate and poorly differentiated tumour, PB histology and DCC. As only seven of our patients received chemoradiotherapy, its benefit could not be evaluated separately. Our study suggests consideration of adjuvant treatment in patients with these high-risk features.

Table 4 Effect of adjuvant treatment on survival

Variables	Adjuvant	No adjuvant	PFS *p* (HR; 95% CI)	OS *p* (HR; 95% CI)
Site				
Ampulla	22	14	0.79 (1.19; 0.34–4.1)	0.5 (1.49; 0.41–5.5)
Bile duct	16	8	0.19 (2.3; 0.65–8.3)	0.006 (5.9; 1.6–20)
Duodenum	6	3	0.83(1.3; 0.12–16.6)	0.47 (0.5; 0.08–1.6)
Pancreas	11	4	0.047 (5.2; 1.02–27)	0.14 (3.3; 0.66–16.6)
T3 and T4 tumours	37	17	0.01 (3.2; 1.3–7.7)	0.001 (5.2; 2.1–12.5)
Histology				
Intestinal	21	13	0.4 (1.6; 0.52–5.55)	0.11 (2.4; 0.66–6.6)
PB	31	14	0.086 (2.3; 0.9–5.88)	0.004 (5; 1.66–12.5)
Node positive	39	14	0.01 (4.1; 1.8–10)	0.001 (4.76; 2–11)
LNR ≥ 0.2	18	8	0.01 (4.76; 1.45–14.3)	0.002 (6.25; 2–20)
Tumour size > 2 cm	29	18	0.03 (2.7; 1.09–7)	0.004 (4.2; 1.6–11)
Grade ≥ 2	41	22	0.063 (2.1; 0.96–4.76)	0.002 (3.5; 1.47–8.3)
R1 resection	13	1	–	–
LVI	33	12	0.012 (3; 1.28–7.1)	0.002 (4.54; 1.8–12.5)
PNI	41	17	0.029 (2.7; 1.1–6.6)	0.001 (5.8; 2.5–14.2)

LNR lymph node ratio, *PNI* perineural invasion, *LVI* lymphovascular invasion, *PB* pancreatobiliary

Table 5 Studies of survival and prognostic factors in periampullary carcinomas

Reference; n	Ampulla		Bile duct		Duodenum		Pancreas		Poor prognostic factors
	Median (mths)	5-yr (%)	Median (mths)	5-yr (%)	Median (mths)	5-yr (%)	Median (mths)	5-yr (%)	
Present study; 95	NR	66	15.6	21	32.3	40	24.9	33	For PFS: LNR ≥ 0.2, LVI; for OS: LNR ≥ 0.2, advanced T stage
Suzuki S [25]; 45			43	40.4					CRP level < 0.3 mg/dl
Bourgouin S [26]; 135		52 (DFS)	18	32 (DFS)	36	43 (DFS)			T4 tumours, PNI and PBD for duodenum, ≥ 3 LN+ and ≥ 4% loss of BMI for ampulla, and T3–T4 for DCC
Williams JL [14]; 510	70.4		40.6		61.2		31.4		PB, PC, histologic grade, LN+
Ethun CG [23]; 1463			40 (DSS)				22 (DSS)		LN+
Courtin-Tanguy [27]; 56			36.9 14.6 (DFS)						Combined organ resection
Serrano PE [24]; 634									Tumour grade, LN+, R1
Buchbjerg T [28]; 28					23	27			
Farid SG [29]; 551									LNR > 0.2, LVI, PNI, R1
Andrianello [30]; 46			31	18					None
He J [13]; 2564	47	45	23	27	54	49	19	18	Tumour type, vein resection, R1, LN+
Klein F [20]; 143		40							LN+, LVI, intraop transfusion, CA 19–9, jaundice, impaired patient condition
Poultsides GA [31]; 122						48			LN+
Kim K [3]; 147		53		50.3		37.5		13	PC, LN+
Hatzaras I [32]; 346	44.3		17.9				17.1		LN+, PNI
Berberat PO [1]; 133	60.9	50.5	42.9	29.9	45.4	24.5			High bilirubin, R1, surgical complications, advanced tumour stages (ampullary)
Bucher P [33]; 45		68							LN+
Di Giorgio A [34]; 64		64.4							Depth of tumour infiltration
Yeo CJ [2]; 242		39		27		59		15	R1, LN+, tumour grade

DFS disease-free survival, *DSS* disease-specific survival, *mths* months, *yr* year, *PB* pancreatobiliary histology, *LNR* lymph node ratio, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN+* positive lymph node, *PC* pancreatic carcinoma, *DCC* distal cholangiocarcinoma, *PBD* pre-operative biliary drainage, R1 R1 resection

The limitations of this study included the following: (a) it was a retrospective study; (b) the origin of tumour, especially in large tumours and those with significant inflammation and fibrosis, could have been misclassified; (c) the tumour site could not be ascertained in three patients; (d) the number of R1 resections are likely to increase with application of a fully standardised protocol [46, 47]; however, this will most likely affect only PCs; (e) in eight patients, the adenocarcinoma could not be further classified into intestinal or PB histology; and (f) the short median follow up and there were patients lost to follow up.

Conclusion

Each subtype of PAC can be considered a separate entity from clinicopathological and survival perspective. AC had lower T stage and R1 resection while PC were larger. AC and DC had better survival compared to PC and DCC. LNR ≥ 0.2 and LVI adversely affected PFS while LNR ≥ 0.2 and advanced T stage adversely affected OS. Adjuvant treatment resulted in significantly better OS in patients with high-risk features which included T stage ≥ 3, LN involvement, LNR ≥ 0.2, LVI, PNI, tumour size > 2 cm, higher grade, PB histology and DCC.

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Conflict of Interest The authors declare that they have no conflict of interest.

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