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Pancreaticoduodenectomy in the Middle East: Achieving optimal results through specialization and standardization

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ABSTRACT

Background: Pancreaticoduodenectomy is a challenging surgical intervention that remains the cornerstone in the treatment of localized peri–ampullary pathologies. The concept of treatment standardization has been well-established in many high-volume centers in the world. Here, we present our experience in pancreaticoduodenectomy from 1994 to 2015.

Methods: We performed a retrospective review of the medical charts of patients who underwent pancreaticoduodenectomy at our institution. Data was entered to SPSS statistical software and analyzed. The Mann–Whitney *U* and Fisher's exact tests were used to report statistical differences between groups.

Results: Of the 370 patients who underwent pacreaticoduodenectomy, 300 were analyzed. The 1-, 3-, 5- and 10-year survival rates were 85%, 35%, 15%, and 7%, respectively with a 30-day mortality rate of 5.0% (15 patients). The median age of the patients was 61 (13–84) years, with 193 (64.3%) males and 107 (35.7%) females. The median operative time was 300 (130–570) min. The median postoperative length of hospital stay was 12 (5–76) days. Thirty-two patients required re-laparotomies; 10 for pancreatic leak, 7 for biliary leak and 15 for control of bleeding. Seventy-five (25.0%) patients developed pancreatic fistulae. Delayed gastric emptying was present in 31 (10.3%) patients. A significant improvement in surgical outcome was observed in cases done after 2008 which indicates the important role of specialized team in surgical management.

Conclusions: The number of patients undergoing pancreaticoduodenectomy has been increasing annually over the past twenty-two years in our institution with results comparable to published series from high-volume centers. Through standardization of surgical techniques and perioperative management carried out by a specialist team, our results continue to improve despite the increasing complexity of cases referred to our unit.

Introduction

Pancreaticoduodenectomy (PD) is one of the most challenging procedures and has been recognized as the treatment option for many peri–ampullary tumors both malignant and benign. In malignant diseases, PD is the only curative option [1–3], despite the fact that most patients present with advanced malignancy, and only 10%–20% of patients are considered resectable [4,5]. The prognosis remains poor with a 5-year survival rate of less than 20% even after surgery [6–8]. We believe that many factors have contributed to the improvement of the outcome of this procedure including centralization into highly specialized center of excellence, advancement of surgical techniques, improvement in intensive care management and the implementing a multidisciplinary approach. In addition, several factors that can predict the prognosis of this disease have been identified, which include nodal involvement, complete resection (R0), size and degree of differentiation of the tumor [4].

Only high-volume centers have shown to have the best long-term outcomes and lowest operative mortality [9,10]. Long-term survival rates vary significantly in various tumor sub-types due to different biological behaviors and spread of each tumor [11]. The concept of treatment standardization in high-volume centers has been well-established in the developed world. However, few reports have been published from other places like the Middle East. We are presenting our experience from 1994 to 2015 in a tertiary

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Table 1
Preoperative serum laboratory results of all patients.

Variables	Data
Sodium (Na) (mmol/L)	137 (122–144)
Cr (mg/dL)	0.8 (0.2–2.7)
Albumin (g/L)	37 (15–53)
Total bilirubin (mg/dL)	3.8 (0.1–33.6)
Aspartate aminotransferase (IU/L)	69 (7–822)
Alkaline phosphatase (IU/L)	251 (22–2337)
White blood count ($\times 10^6$/L)	8200 (3620–31,490)
Hemoglobin (g/dL)	12.5 (7.2–16.9)
International normalized ratio	1 (0.75–2.2)
Carbohydrate antigen 19–9 (U/mL)	86.6 (0.6–45,707)
Carcinoembryonic antigen (U/mL)	2.7 (0.4–8627.8)

Table 2
Intraoperative findings and procedures.

Variables	Data
Pancreatic duct size (mm)	
< 3	71 (23.7%)
3–6	179 (59.7%)
> 6	50 (16.7%)
Pancreatic gland texture	
Soft	84 (28.0%)
Intermediate	141 (47.0%)
Hard	75 (25.0%)
Pancreatic reconstruction	
Invagination	65 (21.7%)
Duct-to-mucosal with stent	104 (34.7%)
Duct-to-mucosal without stent	129 (43.0%)
Pancreaticogastrostomy	2 (0.7%)
Gastrojejunostomy	
Antecolic	293 (97.6%)
Retrocolic	7 (2.3%)
Stapled	180 (60.0%)
Hand sewn	120 (40.0%)
Hepatojejunostomy	
Interrupted	264 (88.0%)
Continuous	36 (12.0%)
Antecolic	281 (93.7%)
Retrocolic	19 (6.3%)

referral care center in the Middle East. The aim of our study is to analyze different factors that would impact the outcome in PD in a developing country in the Middle East. We strongly believe that specialized surgical training and standardization of perioperative management are essential for good outcomes to be achieved in relatively low-resource settings.

Methods

Access to the charts was obtained after the approval of the Institutional Review Board (IRB) at our institution. The work has been reported in line with the STROCSS criteria [12].

The data collected included demographics, clinical presentation, preoperative laboratory results, co-morbidities, American Society of Anesthesiology (ASA) score, medical history, intraoperative parameters, postoperative complications, pathology results, causes of postoperative death, and causes of re-operation.

Data were entered to SPSS Statistical software 24.0 (IBM Corp., Armonk, NY, USA). All the continuous data are displayed as median (range) and categorical variables are presented in absolute numbers and percentages. The Mann–Whitney *U* and Fisher's exact tests were used to test the continuous and categorical variables, respectively. *P* values less than 0.05 were considered significant.

Results

Demographics and clinical presentation

Of the 370 patients, only 300 records were available for review and analysis. The median age was 61 (13–84) years, out of which 193 (64.3%) males and 107 (35.7%) females. Median body mass index (BMI) was 27.1 (15.6–43.7) kg/m^2. Diabetes mellitus was the most common co-morbidity present in 73 (24.3%) patients, followed by coronary artery disease in 30 (10.0%), acute pancreatitis in 6 (2.0%). Of the 300 patients, 145 (48.3%) were smokers. The median ASA score was 2 (1–4). The most common presenting symptoms were jaundice in 228 patients (76.0%) and abdominal pain in 176 (58.7%). Forty-eight (16.0%) patients had a family history of cancer, of which 16 were pancreatic cancer.

Preoperative radiological assessments included computed tomography (CT) scan in 275 patients, magnetic resonance imaging (MRI) for 60 patients, endoscopic ultrasound for 101 patients, and other modalities such as ultrasound and endoscopic retrograde cholangiopancreatogram (ERCP) were also performed for several patients. Preoperative laboratory tests were performed as per recommendations and outlined in Table 1.

Of the 300 patients, 10 (3.3%) received neoadjuvant chemotherapy prior to surgery and 92 (30.7%) required preoperative biliary stenting of which 88 had ERCP and 4 had percutaneous biliary stent placement. Eighteen (6.0%) patients required preoperative blood transfusion due to severe anemia. All patients were evaluated preoperatively for deep vein thrombosis risk; all were put on sequential compressive devices, and 120 (40.0%) patients received low-molecular-weight heparin preoperatively. Piperacillin/tazobactam was the perioperative prophylactic antibiotic of choice in most patients.

Operative technique

Of the 300 PD, 252 (84.0%) underwent standard PD and 48 (16.0%) pylorus preserving PD. The median operative time was 300 (130–570) min. The pancreatic reconstruction was pancreaticojejunal duct-to-mucosa anastomosis without a stent in 129 (43.0%), duct-to-mucosa anastomosis with a stent in 104 (34.7%), pancreatic invagination in 65 (21.7%), and pancreaticogastrostomy in 2 (0.7%). The hepaticojejunostomy was performed in an interrupted fashion in 264 (88.0%) patients and running sutures for the rest. The gastric anastomosis was performed as a gastrojejunostomy in an antecolic fashion in 293 (97.7%) patients and 7 in a retrocolic fashion, with hand sewn in 120 (40.0%) and a stapled anastomosis in 180 (60.0%) patients (Table 2). The majority of anastomosis (281, 93.7%, pancreatic, hepatic and gastric) were performed through a single limb except for 19 (6.3%) patients who underwent a Roux-en-Y gastrojejunostomy.

Postoperative outcome

Postoperative complications occurred in 130 patients. The International Study Group on Pancreatic Fistula (ISGPF) definition graded pancreatic fistulae according to the impact on the patient's hospital course and clinical outcome, and accordingly pancreatic fistula were divided into grades A, B and C. The most important indication of pancreatic leak was the elevated amylase content (> 3 times the upper normal serum value) of the drain fluid, at any time on or after the 3rd postoperative day [13–17]. A total of 75 (25.0%) patients developed pancreatic fistulae, with 43 grade A, 21 grade B and 11 grade C according to the ISGPF definition. Management of collections from pancreatic leak was mainly through percutaneous drainage except in 10 patients who required re-laparotomy for drainage, washout and anastomotic revision. The median drain fluid amylase level on postoperative day 3 was 40 (2–49,250) U/L, and on postoperative day 5 was 33 (0–23,295) U/L. The median

Table 3
Postoperative complications ($n = 130$).

Complications	Data
Pancreatic fistula	75 (25.0%)
Grade A	43
Grade B	21
Grade C	11
Postoperative bleeding	70 (23.3%)
Wound infection	34 (11.3%)
Superficial incisional surgical site infection	29
Deep incisional surgical site infection	5
Intraabdominal abscess	5 (1.7%)
Delayed gastric emptying	31 (10.3%)
Pneumonia	12 (4.0%)
Sepsis	11 (3.6%)
Acute kidney injury	6 (2.0%)
Cardiac complications	5 (1.7%)
Urinary tract infection	5 (1.7%)
Deep vein thrombosis	1 (0.3%)
Biliary leak	21 (7.0%)

Results are mutually inclusive, patients developed more than one complication.

amount of pancreatic drain fluid on postoperative day 3 was 240 (0–1915) mL, and on postoperative day 5 was 200 (0–2900) mL. The range of the number of days for removal of the pancreatic drain was 2–50 days and 18 (6.0%) patients were discharged with the pancreatic drain for more than 30 days. Abdominal drain was removed when the drain fluid amylase concentration was below 100 U/L, or the drainage was less than 50 mL per day. A biliary fistula was diagnosed in patients who had persistent drainage of bilirubin-rich drainage after the 10th postoperative day. Of the 300 patients, 21 had biliary leak, 7 required re-laparotomy to assess the anastomosis. Three different grades of post-pancreatectomy hemorrhage (PPH) (grades A, B, and C) has been established by the International Study Group of Pancreatic Surgery (ISGPS), based on the time of onset, location of bleeding, severity, and clinical impact [18]. A total of 70 (23.3%) patients had postoperative bleeding according to the above definitions, 15 of which (grade C) required re-laparotomy for control of bleeding. The nasogastric tube was discontinued when the fluid output had decreased to less than 200 mL per 24 h, and the median was 4 (1–44) days for the nasogastric tube to be removed. Delayed gastric emptying occurred in 31 (10.3%) patients. The median duration for resuming oral intake was 6 days (1–45). Eighty-five (28.3%) patients received total parenteral nutrition. Twelve (4.0%) patients developed postoperative pneumonia for which they received proper antibiotics. Surgical site infection was observed in 34 (11.3%) patients. Cultures from the wounds were taken and patients were started on proper antibiotics. Twenty-nine infected wounds were classified as superficial incisional surgical site infection, and 5 wounds were classified as deep incisional surgical site infection. Five (1.7%) patients developed wound dehiscence secondary to wound infection, requiring surgical intervention for repair. Five (1.7%) patients developed an intraabdominal abscess requiring a re-laparotomy (Table 3).

Of the 300 patients, 124 (41.3%) were transferred to the intensive care unit (ICU) for monitoring and observation, of which 61 patients stayed for less than 24 h for postoperative monitoring.

Fifteen (5.0%) patients died within 30 days of surgery, with 11 died from septic shock, 4 died secondary to cardiac arrest postoperatively. The 1-, 3-, 5- and 10-year survival rates were 85%, 35%, 15% and 7%, respectively (Fig. 1). The Kapplan–Meier survival analysis was also performed based on the pathology results for malignant tumors (Fig. 2). The median length of postoperative hospital stay was 12 (5–76) days where 28 (9.3%) patients remained in the hospital for more than 30 days.

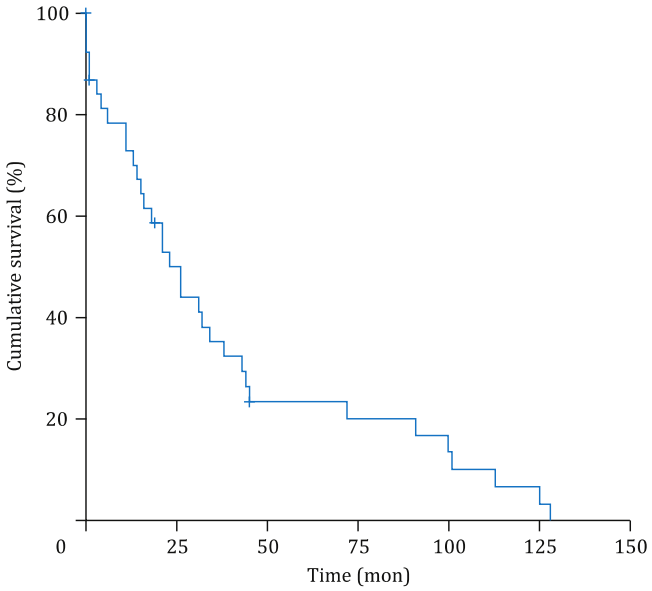

Fig. 1. Kaplan–Meier survival analysis for all patients.

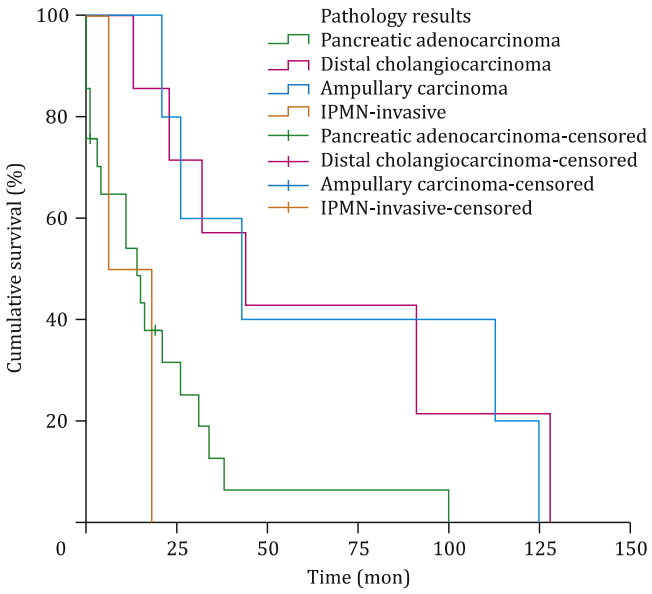

Fig. 2. Kaplan–Meier survival analysis based on cancer type.

Pathology

All pathology specimens were reviewed. Tumor stage was identified according to the TNM system classification [19]. Resection margins of the specimens were considered positive if the tumor was present at the pancreatic neck and the uncinate process, the common bile duct, duodenum, gastric margin of resection, mesenteric artery, or the circumferential margin beyond the anterior pancreatic parenchyma [3]. Of the 300 specimens, 139 (46.3%) were pancreatic adenocarcinoma, 59 (19.7%) ampullary carcinoma, distal cholangiocarcinoma in 28 (9.3%), duodenal cancinoma in 11 (3.7%), nonfunctioning neuroendocrine cancer in 11 (3.7%), functioning neuroendocrine cancer in 2 (0.7%), intra-papillary mucinous neoplasm (IPMN)-invasive type in 3 (1.0%) and cystadenocacinoma in 1 (0.3%). Other malignant types were identified in 13 (4.3%) comprising of mixed malignant pathologies such as pancreatic adenocarcinoma and nonfunctioning neuroendocrine tumor, mixed endocrine-exocrine carcinoma and pancreatic adenocarcinoma.

Table 4
Pathology results ($n=300$).

Pathology	Data
Pancreatic adenocarcinoma	139 (46.3%)
Ampullary carcinoma	59 (19.7%)
Distal cholangiocarcinoma	28 (9.3%)
Duodenal carcinoma	11 (3.7%)
Nonfunctioning neuroendocrine cancer	11 (3.7%)
Intra-papillary mucinous neoplasm-invasive type	3 (1.0%)
Functioning neuroendocrine cancer	2 (0.7%)
Cystadenocarcinoma	1 (0.3%)
Other malignant types	13 (4.3%)
Benign diseases	33 (11.0%)

Also, rare diseases were identified such as pleomorphic spindle cell sarcoma with leiomyosarcomatous differentiation and leiomysarcoma in 6 patients. Thirty-three (11.0%) patients had benign lesions, of which 8 were serous cystadenoma, 8 solid pseudopapillary tumors, 6 chronic pancreatitis, 4 had IPMN-noninvasive type. Seven specimens contained hamartoma, necrosis and inflammatory process, ampullary adenoma and fibrosis (Table 4).

T-stage distributions of the specimens were T1 in 32 (12.0%) patients, T2 in 65 (24.3%), T3 in 149 (55.8%), and T4 in 21 (7.9%). Of the 267 patients with malignant disease, 154 (57.7%) had lymph node involvement. Liver metastases were found in 5 (1.9%) patients who had initially negative frozen section and the final pathology was found to be positive. The median size of the tumor resected was 3 (0.3–18) cm. Median grade of the tumor was 2 (1–4). Perineural invasion was present in 140 (52.4%) patients. Surgical margins evaluated were the proximal pancreatic stump, uncinate process, and the common bile duct. Surgical margins were initially negative in 252 patients (94.4% of the malignant tumors). Margins were positive in 48 resected specimens, however further margins were resected at the time of surgery to ensure negative margins and R0 resections. Of the 48 patients who intraoperatively had positive margin on frozen section, 21 were at the pancreatic stump margin, 19 at the uncinate and 8 at the bile duct margin.

Surgical approach

From 1994 to 1997, 20 PDs were performed at our institution, and they were performed by general surgeons. The results were suboptimal, with a high mortality and morbidity and a prolonged duration of hospital stay. In 1998, a specialized hepatobiliary surgeon was recruited, after which the results improved significantly. The median length of hospital stay was reduced to 16 days from 25 days. In addition, there was a significant improvement in terms of morbidity and postoperative mortality of the patients. From 1998 to 2008, 109 PDs were performed by a single hepatobiliary surgeon. Of the 109 patients, 3 died postoperatively (2.8%). The median blood loss dropped from 800 mL to 400 mL and the median operative time dropped to 335 min. In 2009, another hepatobiliary surgeon joined the program. All PDs since then are being performed by two experienced surgeons specialized in hepatopancreaticobiliary (HPB) surgery, with standardized preoperative, intraoperative and postoperative management. The surgical expertise improved, for instance no vascular resections were performed prior to this period. After 2009, 6 patients had portal vein resection and repair performed for portal vein involvement of the tumor, and the postoperative course was smooth and uneventful for those patients. The median length of hospital stay further decreased to 11 days, and there was an additional improvement in terms of morbidity and mortality. 171 PDs were performed between 2009 and 2015. A total of 3 patients (1.8%) died postoperatively. These patients died secondary to septic shock with multi-organ failure, 1 of which was due to grade C pancreatic fistula. The median blood loss dropped to 300 mL, and the median operative time was reduced from 360 to 280 min (Table 5).

Improvement in service after the induction of hepatobiliary unit in 2009

In 2009, the hepatobiliary service was operated by two experience HPB and liver transplant surgeons. In 2013, our center has established the Liver Transplant and Hepatopancreaticobiliary Unit. Comparing outcomes before and after 2009, we realized a significant improvement. The results are divided into preoperative and intraoperative characteristics. Postoperative outcomes and complications are summarized in Table 6. The length of hospital stay dropped significantly from 20 to 11 days ($P=0.001$). Also the operative time dropped from 348 to 280 h ($P=0.07$). Intraoperative blood loss dropped significantly from 550 mL before 2009 to 300 mL after 2009 ($P=0.008$). Similarly, the need for blood transfusion improved. In addition, the mortality within 30 days dropped from 3.1% to 1.8%, although not statistically significant.

Discussion

Up to our knowledge, this is the largest reported series of outcomes following PD from the Middle East. Our center is considered a high-volume center with a number of cases that has been increasing annually, to reach a median of 32 PDs every year between 2008 and 2015. Our results in regards to overall survival and mortality and morbidity are similar to many high-volume centers in the world [20]. The French surgical association multicenter study of 1296 patients reported a 3.8% rate of major pancreatic leaks [16]; our rate is 3.7% (11/300). We have a 10.3% rate of postoperative delayed gastric emptying whereas it is 12.7% in high-volume centers [13]. We have managed through time and with the hard work of our team to minimize the mortality and morbidity of our patients undergoing PD. There has been incremental improvement in the approaches of the surgical technique leading to less intraoperative bleeding, less pancreatic anastomotic leaks, shortening duration of hospital stay, fewer ICU admission, less blood transfusion, reduced operative time and reduction in the postoperative mortality rates after standardization of the procedure and establishment of hepatobiliary team with two experienced surgeons with a major change in the surgical approach. We believe that the reduction in operative time was a major contributing factor to improving outcomes, as longer operative time has been independently associated with worse perioperative outcomes [21–24]. In addition, several studies have reported the effect of operating at high-volume centers on the surgical and clinical outcomes of patients with reduction of perioperative morbidity and

Table 5
Comparative results from 1994 to 2015.

Variables	1994–1997 ($n=20$)	1998–2008 ($n=109$)	2009–2015 ($n=171$)
Length of hospital stay (d)	25 (10–76)	16 (9–46)	11 (5–37)
Postoperative mortality	5.0%	2.8%	1.8%
Median blood loss (mL)	800 (200–2400)	400 (50–1800)	300 (50–1000)
Median operative time (min)	360 (210–465)	335 (180–570)	280 (130–525)

Table 6
Postoperative outcomes and complications for patients before and after 2009.

Variables	Before 2009 ($n=129$)	After 2009 ($n=171$)	P value
Length of hospital stay (d)	20	11	**0.001**
Operative time (min)	348	280	0.07
Intraoperative blood loss (mL)	550	300	**0.008**
Transfusions			**0.003**
Intraoperative	37 (28.7%)	25 (14.6%)	
Postoperative	32 (24.8%)	7 (4.1%)	
Time to remove nasogastic tube (d)	7.9	6.3	0.46
Time to remove drain (d)	11.6	8.3	0.31
Morbidity			
Cardiac complications	2 (1.6%)	2 (1.2%)	0.54
Wound complications			0.47
Superficial	6 (4.7%)	15 (8.8%)	
Deep	1 (0.8%)	2 (1.2%)	
Intrabdominal collection	8 (6.2%)	7 (4.1%)	0.13
Sepsis/septic shock	3 (2.3%)	3 (1.8%)	0.83
Delayed gastric emptying	10 (7.8%)	13 (7.6%)	0.21
Pancreatic fistula			0.99
Required invasive intervention	6 (4.7%)	5 (2.9%)	
No invasive intervention	17 (13.2%)	37 (21.6%)	
Mortality within 30 days	4 (3.1%)	3 (1.8%)	0.99

mortality [25,26]. Also, it has been shown that mortality can be reduced by improving patient selection, optimizing postoperative nutritional status, and accurate staging [27]. The number of operations performed has increased at our institution since the establishment of the HPB unit. There is also a crucial role for the multidisciplinary team work, with a clear decision plan provided to patients peri– and postoperatively, hence improving outcomes.

In conclusion, PD is a complex surgical operation with high rate of mortality and morbidity, but remains the only chance to cure patients with pancreatic cancer. With the advancement in surgical technique and the multidisciplinary approach to these patients, PD has become safer, and is recognized as the gold standard for treating peri–ampullary pathologies. The concept of treatment standardization in high-volume centers has been well-established in the developed countries and this is what we have achieved at our institution. PD should not be performed in a scattered way in several hospitals; all PD should be performed in specialized hepatobiliary center by experienced hepatobiliary surgeons.

Contributors

FW and Khalife M proposed the study. NH, ZA, MD, and SA performed the research and wrote the first draft. Kanso M and JRF analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. FW is the guarantor.

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Ethical approval

This study was approved by the Institutional Review Board at the American University of Beirut Medical Center (SUR.WF.02).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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