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Gastric cancer following pancreaticoduodenectomy: Experience from a high-volume center and review of existing literature

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ABSTRACT

Background: Prolonged survival of patients after pancreaticoduodenectomy can be associated with late complications due to altered gastrointestinal anatomy. The incidence of gastric cancer is increasingly reported. We set out to examine our experience with gastric cancer as a late complication after pancreaticoduodenectomy with a focus on incidence, risk factors, and outcomes.
Methods: We queried our prospectively collected institutional database for patients that developed gastric cancer after pancreaticoduodenectomy and conducted a systematic review of the literature.
Results: Our database revealed 6 patients who developed gastric cancer following pancreaticoduodenectomy, presenting with a mean age of 62.2 years and an even sex distribution. All of those patients underwent pancreaticoduodenectomy for malignant indications with an average time to development of metachronous gastric cancer of 8.3 years. Four patients complained of gastrointestinal discomfort prior to diagnosis of secondary malignancy. All of these cancers were poorly differentiated and were discovered at an advanced T stage (≥3). Only half developed at the gastrointestinal anastomosis. Four underwent surgery with a curative intent, and 2 patients are currently alive (mean postgastrectomy survival = 25.5 months). In accordance with previous literature, biliopancreatic reflux from pancreaticoduodenectomy reconstruction, underlying genetic susceptibility, and adjuvant therapy may play a causative role in later development of gastric cancer.
Conclusion: Long-term survivors after pancreaticoduodenectomy who develop nonspecific gastrointestinal complaints should be evaluated carefully for complications including gastric malignancy. This may serve as an opportunity to intervene on tumors that typically present at an advanced stage and with aggressive histology.

INTRODUCTION

The observation that gastric cancer develops remotely after partial gastrectomy for benign indications, such as peptic ulcer disease, has been reported in the literature for decades [1–9]. However, the underlying mechanism of malignant transformation remains an area of active investigation, without a clearly delineated cause. Posited mechanisms attributed to physiologic alterations after surgery include hypochlorhydria, bacterial colonization, increased carcinogenic nitrate-derived compounds, and biliary reflux which damages the gastric mucosal barrier [10–15]. In addition, tissue damage caused by the surgery itself, chronic ulcers, or the presence of permanent suturing material has been suggested as possible contributing factors [16–19]. Since partial gastrectomy can be a component of several other operations, those risk factors might be present after a variety of surgical procedures.

One such procedure increasingly performed in the modern era is pancreaticoduodenectomy (PD), or the Kausch-Whipple procedure. Historically limited to the management of pancreatic ductal adenocarcinoma (PDAC), the indications for PD have expanded to include symptomatic benign and premalignant conditions as operative technique and perioperative care have been refined [20–23]. Contemporary indications for PD now include neuroendocrine tumors, intraductal papillary mucinous neoplasms (IPMNs), and chronic pancreatitis [20,23,24]. As the survival of these conditions is significantly longer than patients undergoing PD for PDAC, more patients are at risk of experiencing long-term complications associated with this procedure

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[25–29]. In addition, improved systemic chemotherapeutics for PDAC and administration of neoadjuvant treatment have led to an increased survival in the postsurgical PDAC cohort [30,31]. Given the altered anatomy after PD, many of the mechanisms thought to contribute to gastric cancer development after partial gastrectomy are present after PD, such as biliopancreatic secretion reflux and the potential for chronic gastrojejunostomy (or duodenojejunostomy) inflammation. Viewed alongside the historical experience of gastric cancer arising after partial gastrectomy, one would suspect that there is potential for development of a secondary gastric cancer after PD.

The currently available literature lacks guidance on expectations for surgeons and patients entertaining PD in the setting of improved survival. We therefore reported our experience with secondary gastric cancer after PD and conducted a detailed analysis of each case to study patient, operative, and disease-specific factors that may contribute to this outcome. To place our experience in appropriate context, we supplemented our institutional findings with a comprehensive review of the global literature to examine the experience of other high-volume pancreatic surgery centers with this entity.

METHODS

We conducted a structured literature review using PubMed. The database was searched for the following combinations of terms: *whipple AND gastric cancer*, *pancreaticoduodenectomy AND gastric cancer*, *PDAC AND gastric cancer*, *whipple AND stomach*, *pancreaticoduodenectomy AND stomach*, and *PDAC AND stomach*. These results were supplemented with results garnered by using pancreatoduodenectomy in place of PD. Relevant articles were reviewed and data were abstracted. To ensure capture of the sum total of reported cases, a survey of each included article's references was undertaken and added to the literature review. Articles published in languages other than English underwent review by physicians and surgeons that are native speakers of those languages.

A comprehensive review of our prospectively collected institutional pathology database was conducted to identify patients that underwent PD between 2000 and 2018. This was cross-referenced with a review of patients with a subsequent histopathologic diagnosis of gastric malignancy. The database was queried, again with the use of appropriate combinations of keywords such as *whipple*, *pancreaticoduodenectomy*, *signet cell cancer*, *gastric cancer*, and *PDAC*. Patients met the inclusion criteria if they were diagnosed with gastric cancer more than 1 year after PD to minimize the likelihood of synchronous disease left in situ at the time of PD. For inclusion in our series, pathological diagnosis needed to confirm that both entities arose independently from each other (eg, by morphology and histopathologic staining). For each case, detailed review of the clinical course and diagnostic findings, such as endoscopy and cross-sectional imaging, confirmed that the secondary malignancy was not recurrence or residual disease. Patients undergoing PD for both benign and malignant etiologies were included. Background demographics (sex, race, age, date of death, medical history); pathological diagnoses and characteristics (including tumor-node-metastasis classification, grading); and other relevant clinical information, such as surgical procedure, adjuvant treatment, and presenting symptoms, were

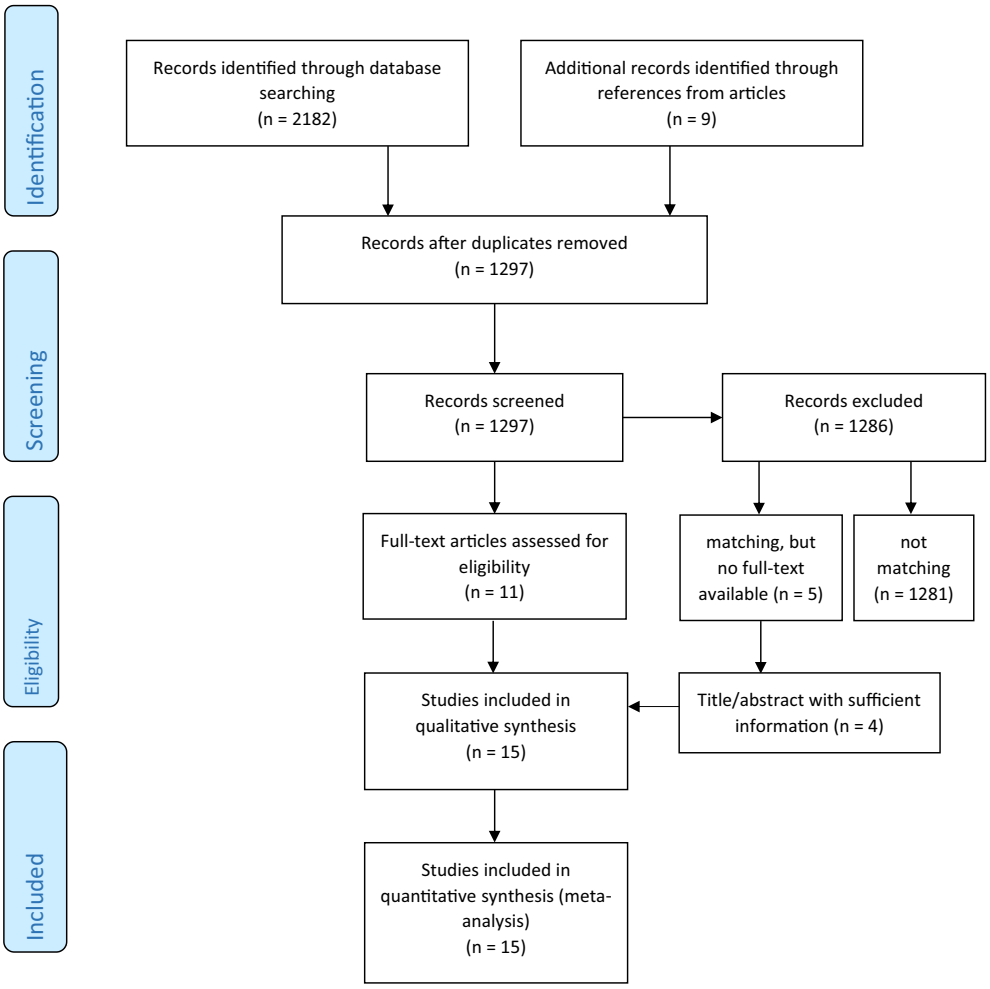

Fig 1. Search strategy and results.

Table I
Previous publications on gastric cancer after PD

First author	*Published (y)*	*Origin/language*	*Number of cases (sex, age*)*	*Full text available*	*Indication for PD*	*Treatment*	*Gastric anastomosis/pancreatic anastomosis*	*Interval (y)*	*Gastric cancer histology (grade)*	*Localization in stomach*
Tatsuzawa [36]	1995	Japan/Japanese	1 (male, 64)	Yes	IPMN	PPPD	−/PG	4	Adenocarcinoma in situ (G1)	Posterior wall of lower body
Kaneda [37]	1996	Japan/English	1 (female, 65)	Yes	Chronic pancreatitis	PPPD	Billroth I/PG	2	Adenocarcinoma (G2)	Antral anterior wall
Yamamoto [58]	1999	Japan/Japanese	1 (male, 47)	Yes	Chronic pancreatitis	Duodenum-preserving head resection	Roux-en-Y/PJ	5	Signet ring cell carcinoma (G3)	Body, antrum
Wenk [59]	2000	Germany/German	1 (male, 65)	Yes	Distal cholangiocarcinoma	PD	Billroth II (Child)/PJ	2	Signet ring cell carcinoma (N/A)	No details
Manabe [60]	2001	Japan/English	1 (male, 66)	Yes	Distal cholangiocarcinoma	PD	Billroth II/unknown	5	Admixture† (G3)	Lesser curvature
Taniguchi [61]	2001	Japan/	1	No	–	PPPD	–	–	Gastric cancer (unspecified)	–
Ohashi [62]	2001	Japan/	1	No	Carcinoma of papilla of Vater	PPPD	–	–	Gastric cancer (unspecified)	
Emoto [40]	2002	Japan/Japanese	1 (male, 68)	Yes	Mucinous cystadenocarcinoma	PPPD	Billroth I/PG	4	Adenocarcinoma (G2)	Greater curvature of pylorus
Mihara [41]	2005	Japan/English	1 (female, 59)	Yes	Distal cholangiocarcinoma	PPPD	Unknown/PG	4	Adenocarcinoma (tubular; G2)	PG anastomosis
Furukawa [63]	2007	Japan/Japanese	1 (male, 66)	Yes	Distal cholangiocarcinoma	PPPD	Billroth II/PJ	7	Adenocarcinoma (G1)	Lesser curvature
Kassahun [39]	2008	Germany/English	1 (male, 62)	Yes	PDAC	PD	Billroth II/unknown	5	Signet ring cell carcinoma (G3)	GJ anastomosis
Yamada [64]	2014	Japan/Japanese	1 (male, −)	Abstract only	PDAC	PD	Modified Child/unknown	15	Gastric cancer (unspecified)	Cardia
Hijikawa [38]	2015	Japan/Japanese	1 (male, 65)	Abstract only	Chronic pancreatitis	PD	GJ/unknown	17	GI stromal tumor	GJ anastomosis
Bouquot [33]	2017	France/English	2 (male, 38; female, 68)	Yes	Ampullary adenocarcinoma (1), PDAC (1)	PD (1), TP (1)	Billroth II (2)/PG	19 (1), 10 (1)	Signet ring cell carcinoma (G3)	GJ anastomosis
Sonoda [34]	2019	United States/English	6 (male [4], female [2], 39–63)	Yes	PDAC (5), distal cholangiocarcinoma (1)	PD	Billroth II (modified Child)/PJ	9.3 (median; range 1.9–15.9)	Signet ring cell carcinoma (4), adenocarcinoma (2) (G3 [6])	GJ anastomosis (5), body (1)

GJ, gastrojejunostomy; *TP*, total pancreatectomy.
* Age at initial surgery.
† Admixture of poorly differentiated adenocarcinoma of medullary type and foci of malignant lymphoma of the diffuse, medium-sized cell type.

retrieved from the database with subsequent review of the medical record as indicated.

The study was approved by the Johns Hopkins institutional review board. The data were collated using Excel (Microsoft Co, Redmond, WA), and statistical analysis was performed using IBM SPSS Statistics (Version 25; IBM Co, Armonk, NY). Descriptive statistics are presented as means with corresponding minimum and maximum values.

RESULTS

Literature Review. Our search strategy yielded 2182 articles, which subsequently underwent title, abstract, and full-text review following the preferred reporting items for systematic reviews and meta-analyses recommendations as outlined below (Fig 1) [32]. In total, 21 cases of metachronous gastric cancer after PD were reported in 15 articles, with only 2 studies reporting more than a single case [33,34]. The majority of these studies originated from Japan (11/15), and reports from Western institutions were found to be rare. Of note, 5 of the 11 articles with full text available were only published in the language of their institution's origin (4 Japanese; 1 German) and were reviewed by physicians (KF, MP) that are native speakers of these languages. A summary is shown in Table I.

Patient's age at initial surgery ranged from 38 to 68 years, with the majority being male (14/21). The main indication for PD was malignancy, predominantly PDAC (8) and distal cholangiocarcinoma (5). However, other pre- and nonmalignant indications, such as IPMN and chronic pancreatitis, have also been reported. Traditional PD was performed in 12 cases, pylorus-preserving pancreaticoduodenectomy (PPPD) in 7 cases, duodenum-preserving pancreatic head resection in 1 case, and total pancreatectomy in 1 case. Reconstruction methods were not universally reported but comprised mainly Billroth II for gastrojejunal anastomosis and pancreaticojejunostomy (PJ) to reestablish pancreatogastrointestinal continuity. In fewer cases, Billroth I and pancreaticogastrostomy (PG) were used to reestablish gastrointestinal (GI) continuity.

Gastric cancer was discovered between 1.9 and 19 years after initial surgery. Histopathologic diagnosis of gastric cancer included signet ring cell carcinoma (SRCC; 8 cases) and adenocarcinoma (8 cases). Intriguingly, components of lymphoma have been described in 1 case and GI stromal tumor was diagnosed in another case.

Institutional Database. There were 6 patients identified in our database with metachronous development of gastric cancer. These patients underwent PD between 2000 and 2015 at our institution at a mean age of 62.2 years (range, 48–79). A total of 4414 PDs were done during the time period. Cases of gastric cancer after PD occurred in an equal number of men and women (3 male, 3 female), and all were white. The majority had an unremarkable social history (1 smoker, no alcoholism). Three of the 6 patients in our cohort had been previously treated for a malignancy (breast, colon, and tonsil), including 1 patient with Lynch syndrome (case 6). Other relevant medical history included Crohn disease in 1 patient (case 4). One patient had a positive family history of pancreatic cancer (case 3).

All of our patients underwent surgery for a malignant indication; these included PDAC (2), duodenal adenocarcinoma (2), distal cholangiocarcinoma (1), and ampullary carcinoma (1). Tumor size at surgery was up to 2.5 cm (range, 0.1–2.5 cm). The classic PD technique (Whipple procedure) was used in 4 cases and PPPD was used in 2 cases, all using a Billroth II gastrojejunostomy or duodenojejunostomy for reconstruction. For drainage of the remnant pancreas, PJ was performed in all cases. One patient (case 6) underwent completion of colectomy and subsequent ileorectal anastomosis because of a synchronous colonic adenocarcinoma. Surgical margins of PD were free from tumor on final pathological diagnosis for all patients. Four patients received adjuvant chemotherapy and radiation therapy. Surgical reintervention was required for 1 patient (case 1) who had a gastric outlet obstruction

Table II
Institutional cohort—indications for PD and patient characteristics

Case	*Sex (age*)*	*Race*	*BMI*	*DM*	*MHx of cancer*	*Genetic disease*	*FHx*	*Smoking/drinking*	*Indication for PD*	*Date of PD*	*Surgery type*	*Anastomosis*	*T stage (size)*	*N stage (# nodes)*	*Grade*	*Margin*	*Adjuvant therapy (type)*
1	Male (48)	White	14.6	No	Oral squamous cell cancers	No	No	Yes/regularly	Ampullary carcinoma	2000	PD	BII + PJ	T3 (2 cm)	N1 (18/33)	G3	Negative	Yes (CRT)
2	Female (79)	White	UK	No	Breast cancer	No	UK	UK	Distal cholangiocarcinoma	2002	PPPD	BII + PJ	T3 (2 cm)	N0 (0/18)	G2–3	Negative	No
3	Female (55)	White	15.2	No	No	No	Yes	No/no	PDAC	2007	PD	BII + PJ	T3 (2 cm)	N1b (6/38)	G3	Negative	Yes (CRT)
4	Male (48)	White	15.7	No	No	No	No	No/rare	PDAC	2007	PPPD	BII + PJ	T1 (<1 mm)	N0 (0/25)	UK	Negative	Yes (CRT)
5	Male(71)	White	20.4	No	No	No	No	No/rare	Duodenal adenocarcinoma	2010	PD	BII + PJ	T2 (1.5 cm)	N0 (0/23)	G2	Negative	Yes (CRT)
6	Female (72)	White	15.7	No	Colon and endometrial cancer	Yes (HNPCC)	No	No/regularly	Duodenal adenocarcinoma	2015	PD	BII + PJ	T2 (2.5 cm)	N0 (0/12)	G2	Negative	No

BII, Billroth II; *BMI*, body mass index; *CRT*, chemoradiotherapy; *DM*, diabetes mellitus; *FHx*, family history; *HNPCC*, hereditary nonpolyposis colon cancer; *MHx*, medical history; *UK*, unknown.
* Age at initial surgery.

secondary to a radiation stricture, which required a Roux-en-Y gastrojejunostomy. Results are summarized in Table II.

Gastric cancer was diagnosed at a mean interval of 8.3 years (range, 1.5–17) after PD. Four of the 6 patients presented with symptoms which included dysphagia, nausea, vomiting, reflux, and early satiety. Gastrojejunal anastomosis was the most common location (3 in total, 1 with diffuse infiltration), with others located at the gastroesophageal junction (1) as well as the body and fundus (2). Signet ring cell cancer was diagnosed in 4 patients, adenocarcinoma with mucinous features and squamous cell carcinoma in 1 patient, respectively. All potential cases underwent a pathology review by a dedicated expert pathologist to confirm gastric origin of tumor as opposed to recurrence of the pancreatobiliary primary (Fig 2). Tumor stages were T3 or higher in all cases, with tumor sizes ranging between 2.7 and 8 cm, except for case 3 in which the diffuse growth pattern did not enable determination of final tumor size (Fig 3). All tumors were graded as "poorly

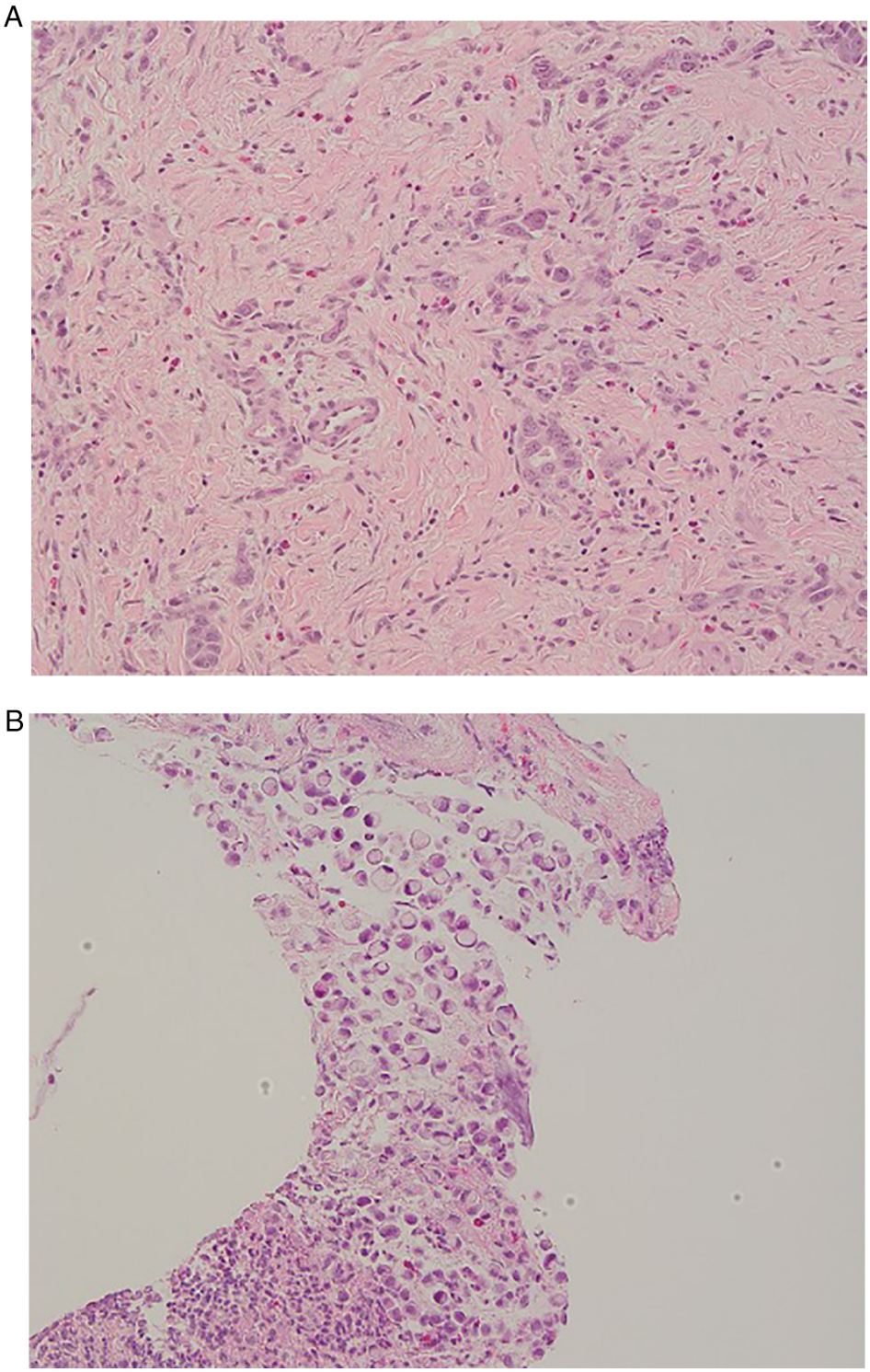

Fig 2. A, Patient 1. Ampullary carcinoma. Slide derived from surgical specimen. B, Patient 1. SRCC at gastroanastomotic site 17 years after Whipple procedure. Biopsy.

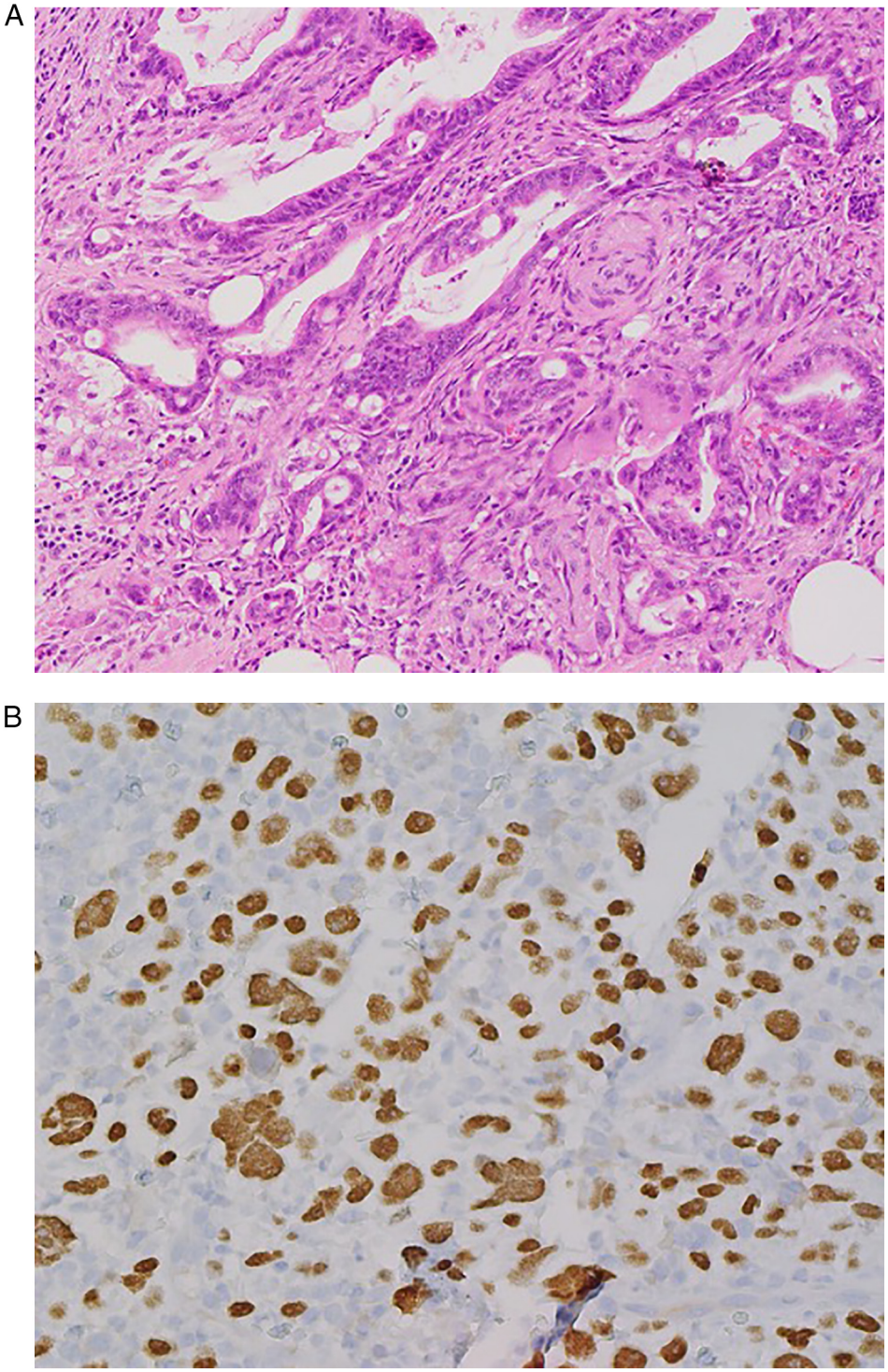

Fig 3. A, Patient 5. Duodenal adenocarcinoma with associated villous adenoma (not shown). Surgical specimen. B, Patient 5. Squamous cell carcinoma located on gastroesophageal junction 5 years after Whipple procedure. p40 staining. Biopsy.

differentiated" (G3) on final pathological diagnosis. Nodal involvement was present in 4 patients and lymphovascular invasion was noted in 3 patients at histopathologic assessment. Four patients underwent surgery (3 total gastrectomy, 1 partial gastrectomy) for treatment of the gastric malignancy. Reconstruction after total gastrectomy was commonly performed by converting the Billroth II from PD into a Roux-en-Y esophagojejunostomy. Despite radical surgical resection, 2 of 4 patients were diagnosed with persistent disease at the surgical margins on final pathology (both with diffuse-type disease and a positive proximal margin after total gastrectomy). In 1 of these (case 2), the radial margins were also positive and were reflective of the palliative intent of the operation in the setting of a symptomatic 84-year-old patient. The second patient (case 3) presented with a single cluster of atypical cells of less than 0.1 mm present within a lymphovascular space. Although suspicious for carcinoma, it was too small for definitive characterization. Only 1 patient received adjuvant

therapy after surgery for metachronous gastric cancer. Two patients were alive at the time of data abstraction, presenting with a survival of 15 and 36 months after gastric surgery. Results are summarized in Table III.

DISCUSSION

Here we report the largest known series of metachronous gastric cancer in patients previously undergoing PD. Similar to the development of gastric cancer after partial gastrectomy for other indications, the results from our institution indicate that gastric cancer after PD is a relatively rare and late event (>5 years on average). The majority of our patients had nonspecific GI complaints prior to diagnosis, and all had gastric cancer with aggressive disease biology. Similar findings were noted on review of the literature, without a clear precipitating factor. Development of gastric cancer is likely multifactorial and is an important consideration when evaluating patients with GI complaints after PD. Given the numerous studies showing an elevated long-term risk of gastric cancer after gastrectomy for ulcer disease and the distinct pattern of tumor biology and histology documented after PD, it is unlikely that our reported cases are the sole result of incidental findings [1–6,35]. Following the steady but sporadic single-case reports from institutions abroad, there seems to be emerging evidence for causality, with a recent study from the MD Anderson group presenting their experience [34]. When recognizing that long-term postsurgical patients are susceptible to loss in follow-up, the true incidence of metachronous gastric cancer may likely be higher than what we observed. Although the incidence may increase over time as PD is performed more commonly for premalignant indications, the awareness of this potential complication through publications such as ours may improve data collection prospectively and serve to better elucidate drivers of this rare disease.

We noted several interesting findings in our work. First, all patients in our cohort developed grade 3 gastric tumors reflecting a poorly differentiated morphology (including 4 with signet ring cells). These findings support those of recent publications reporting poorly differentiated adenocarcinomas and signet ring cell morphology [33,34]. In keeping with this poor disease biology, frequent nodal spread and lymphovascular invasion were commonly seen in our cohort. Second, although we initially hypothesized encountering a number of long-term survivors from PD performed for benign indications, none of our patients underwent PD for a benign or premalignant condition. Although this is in accordance with the majority of cases previously reported, gastric cancer after PD for IPMN or chronic pancreatitis has been reported [36–38]. This may be at least partly explained historically due to PDAC being the predominant indication for PD. However, the bias toward patients undergoing PD for underlying malignancy suggests that an unanticipated predisposition may exist in this cohort. Options include an unappreciated genetic predisposition, adverse effects from administered adjuvant chemoradiation, or other age-related risks. This finding may damper the enthusiasm for a hypothesis suggesting a mechanism of disease development relating solely to biliopancreatic reflux in long-term survivors. For if this hypothesis was the sole driver of disease, gastric cancer after PD for benign indications (a large cohort of long-term survivors) would be expected to be found more commonly.

There are a number of risk factors which may contribute to the development of gastric cancer after PD. As discussed above, one hypothesis claims that pancreaticobiliary reflux through the GI anastomosis promotes tumorigenesis in the remnant stomach [39]. Three of our 6 cases had involvement of the GI anastomotic site, supporting mucosal damage and chronic inflammation as potential contributing etiologies. Although it is likely that biliopancreatic reflux is not the only driver of disease, significant reflux of biliary and pancreatic secretions is inherent to the Billroth II reconstruction that all in our cohort received [2]. It is important to note that this method has been the standard at our center and others for decades, barring a

Table III
Institutional cohort–clinicopathological characteristics and treatment of metachronous gastric cancer

Case	*Indication for Whipple*	*Time to diagnosis of gastric cancer (y)*	*Symptoms*	*Gastric cancer histology*	*T stage (size)*	*N stage (# nodes)*	*Metastatic disease*	*Grade*	*Location of gastric cancer*	*Treatment*	*Margins (for those undergoing surgery)*	*Adjuvant treatment (type)*	*Deceased*
1	Ampullary carcinoma	17	Yes	SRCC*	Unknown (5 cm)	Unknown	–	G3	GJA	Stent	No surgery	No	Yes
2	Distal cholangiocarcinoma	4	Yes	SRCC†	T3 (8 cm)	N3 (20/25)	–	G3	Fundus, body, antrum	Total gastrectomy	Positive	No	Yes
3	PDAC	11	Yes	SRCC†	T3 (unknown)	N2 (3/5)	–	G3	Diffuse w/ GJA	Total gastrectomy	Positive	Yes (chemotherapy)	No
4	PDAC	11	Yes	SRCC†	T4a (>5 cm)	N3a (7/31)	–	G3	GJA	Total gastrectomy	Negative	No	Yes
5	Duodenal adenocarcinoma	5	No	SCC*	T3 (6 cm)	N2–3 (unknown)	Yes (M1)	G3	GEJ	Palliative	No surgery	No	Yes
6	Duodenal adenocarcinoma	1	No	Adenocarcinoma†	T3 (2.7 cm)	N0 (0/7)	–	G3	Fundus, body	Partial gastrectomy	Negative	No	No

GEJ, gastroesophageal junction; *GJA*, gastrojejunal anastomosis; SCC, squamous cell carcinoma.
* Origin of specimen: biopsy.
† Origin of specimen: resectate.

brief period in which a Braun was additionally constructed. None of our cases arose during the period in which a Braun was performed. In our literature review, gastric cancer is identified following alternative technical methods for GI reconstruction [37,40,41].

Interestingly, in light of the proposed mechanism of biliopancreatic reflux, the use of PPPD in our cohort did not appear to be protective. Of note, combination of pylorus preservation and PJ (rather than PG) has been suggested to be a potential method to reduce gastric irritation from pancreatobiliary reflux. Reports of metachronous gastric cancer in patients with this reconstruction technique have not been described prior to our experience (cases 2 and 4). Although anatomy of the remnant stomach can be heavily altered and thus determination of a location of gastric neoplasia can be somewhat challenging, occurrence at a locus distant from anastomosis, such as gastroesophageal junction in our cohort (case 5), suggests potential drivers beyond biliopancreatic reflux for some patients.

Established nonsurgical risk factors for both pancreatic and gastric cancer, such as smoking or obesity, are not universally linked to the development of metachronous gastric cancer after PD [42–47]. Similarly, diabetes and alcohol intake have not been identified to play a particular role. Although the predominance in early reports from Japanese institutions may be suggestive of ethnicity as a risk factor, given the most recent literature, this hypothesis too seems unlikely. Instead, germline mutations may drive a cohort for some of the patients, as 1 patient in our cohort had Lynch syndrome with *MSH 2* gene mutation. Additionally, the MD Anderson group reported 1 patient with *BRCA* mutation and 1 with Lynch syndrome in their cohort [34]. One patient in our cohort had a family history of pancreatic cancer, which may also be indicative of an underlying genetic predisposition [48–50]. Moving forward, increasing utilization of germline and somatic sequencing of tumors may assist in clarifying the role of this potential risk factor.

Another possible contributing factor is the use and type of adjuvant therapy for the primary cancer. Chemotherapy, radiation, or a combination of both is recommended after surgical resection for many malignancies, including PDAC [51–54]. Radiation is of particular interest, as there is a well-documented association between radiation and remote development of secondary malignancy [55,56]. However, this hypothesis is somewhat contradicted by the reported development of metachronous gastric cancer after gastric resection for benign indications. All cases of secondary gastric cancer after PD were detected within an interval of 20 years, with the majority well within this follow-up period. In contrast, the risk of metachronous gastric cancer after gastrectomy for peptic ulcer has been reported to increase after about 15 to 20 years from surgery [1–6,8,9,35]. Given the magnitude of the surgery required for PD and the associated physiologic and anatomic alterations, such as nonanatomic drainage of bile and pancreatic secretions, there may be significantly different changes to the microenvironment and microbiology in comparison to gastric resection for ulcer disease. The underlying drivers of gastric cancer development may, in fact, be different following PD than for patients undergoing resection for benign gastric disease.

In general, incidence of vague GI symptoms is high in patients following Whipple procedure. Nevertheless, 4 of 6 patients describe a change in GI symptoms that eventually led to the diagnosis of a secondary cancer. The symptoms described in this cohort are similar to those described by patients with newly diagnosed primary gastric malignancy; most commonly, reported symptoms include nausea and early satiety (not displayed). Because these symptoms are relatively nonspecific, particularly after PD, clinical diagnosis is difficult and can commonly be delayed. Our data suggest that new GI complaints in patients with remote history of PD should prompt further workup with early consideration of upper endoscopy. This modality may detect serious long-term complications after PD that include metachronous gastric cancer, as well as much more frequent complications such as anastomotic ulcer, primary disease recurrence, stricture, and others. Both our data and reports in the literature demonstrated a long interval between PD and development of gastric cancer (up to 19 years), suggesting that regular follow-up should be continued well beyond 5 years. This is particularly important for patients undergoing PD for benign conditions, as they may not be followed in a manner akin to patients with malignancy.

Although we used a large database from a high-volume institution, our results are clearly limited by a small number of affected patients. Given the total of 4414 PDs performed at our institution during the observation period, metachronous gastric cancer is an uncommon event (0.14%), which is also borne out by the infrequent reports in the literature. Obtaining a large number of patients to determine factors that contribute to metachronous gastric cancer is also hindered by structural problems such as misclassification of primary gastric cancer as recurrence or metastasis of initial disease, patients who had late follow-up at other institutions, or those lost to follow-up in general. Therefore, it is likely that the true number is in fact higher than our dataset suggests. This problem could be addressed by examining large, national administrative datasets in future studies. Also limiting our analysis of risk factors is the lack of clinical and historical information detailing dietary habits or the presence of *Helicobacter pylori* in our cohort.

In conclusion, almost 1 century after the first description of gastric cancer following gastrectomy for ulcer disease, we report our experience with the development of gastric cancer after PD [57]. We demonstrate that this is a rare event which is likely to be related, at least in part, to the anatomic and physiologic changes caused by the procedure. Further study of risk factors is needed to clarify causative drivers. Metachronous gastric cancer may become more frequently encountered after PD as the indications for PD expand and as the number of long-term survivors grows. Our experience, in the context of that provided by a comprehensive analysis of the literature, suggests that gastric cancer is a late complication presenting with particularly aggressive biology. Nonspecific GI symptoms may be a harbinger of a new malignancy. For post-PD patients, this should prompt further urgent workup with endoscopy because this may offer an opportunity for early intervention.

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None.

Author Contributions

MJP, MF, and RAB designed the study and acquired data. MJP, MF, RKS, NR, FvO, JH, JY, and RAB interpreted data. LDW and RHH provided pathological background data and expertise, and KF re-reviewed the slides. RAB, JH, CLW, JLC, MJW, and WB performed the surgical procedures. MJP, MF, RKS, and RAB wrote the manuscript. All authors critically reviewed the manuscript. LDW, CLW, and JP provided supervision, led by RAB.

Conflict of Interest

None.

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