



# Surgical Outcomes After Pancreatic Resection of Screening-Detected Lesions in Individuals at High Risk for Developing Pancreatic Cancer

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Received: 28 December 2018 / Accepted: 10 April 2019 / Published online: 13 June 2019  
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## Abstract

**Background** Screening high-risk individuals (HRI) can detect potentially curable pancreatic ductal adenocarcinoma (PDAC) and its precursors. We describe the outcomes of high-risk individuals (HRI) after pancreatic resection of screen-detected neoplasms.

**Methods** Asymptomatic HRI enrolled in the prospective Cancer of the Pancreas Screening (CAPS) studies from 1998 to 2014 based on family history or germline mutations undergoing surveillance for at least 6 months were included. Pathologic diagnoses, hospital length of stay, incidence of diabetes mellitus, operative morbidity, need for repeat operation, and disease-specific mortality were determined.

**Results** Among 354 HRI, 48 (13.6%) had 57 operations (distal pancreatectomy (31), Whipple (20), and total pancreatectomy (6)) for suspected pancreatic neoplasms presenting as a solid mass (22), cystic lesion(s) (25), or duct stricture (1). The median length of stay was 7 days (IQR 5–11). Nine of the 42 HRI underwent completion pancreatectomy for a new lesion after a median of 3.8 years (IQR 2.5–7.6). Postoperative complications developed in 17 HRI (35%); there were no perioperative deaths. New-onset diabetes mellitus after partial resection developed in 20% of HRI. Fourteen PDACs were diagnosed, 11 were screen-detected, 10 were resectable, and 9 had an R0 resection. Metachronous PDAC

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This work was presented as a SSAT Plenary presentation at the Digestive Disease Week 2018, Washington D.C. on June 3, 2018.

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All authors have met the criteria for authorship including (1) providing substantial contributions, (2) drafting the work and/or critically revising the intellectual content, (3) providing final approval, and (4) providing agreement to be accountable for all aspects of the work.

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developed in remnant pancreata of 2 HRI. PDAC-related mortality was 4/10 (40%), with 90% 1-year survival and 60% 5-year survival, respectively.

**Conclusions** Screening HRI can detect PDAC with a high resectability rate. Surgical treatment is associated with a relatively short length of stay and low readmission rate, acceptable morbidity, zero 90-day mortality, and significant long-term survival.

**Clinical Trial Registration Number** NCT2000089

**Keywords** Pancreatic cancer · Early detection · Screening · Surgical outcomes

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death in the USA and is expected to become the second leading cause of cancer-related death in the USA by the year 2020, surpassing colorectal cancer. The majority of PDACs present with advanced disease.<sup>1</sup> The overall 5-year survival rate remains low, at only 9%, with only 20% of patients surviving one year.<sup>2</sup> Pancreatic screening and early detection are considered by expert opinion and available evidence<sup>3–6</sup> to be the best way to improve clinical outcomes. About 10% of patients with PDAC have a family history of pancreatic cancer or a known hereditary cancer-associated syndrome.<sup>7</sup> Individuals at high risk (HRI) for PDAC include unaffected relatives from familial pancreatic cancer (FPC) kindreds with at least one affected first-degree relative and one affected second-degree relative and individuals who carry deleterious mutations in familial pancreatic cancer genes.<sup>4</sup> The familial pancreatic cancer genes include *BRCA2*, *ATM*, *PALB2*, *BRCA1*, *CDKN2A* (familial atypical multiple mole melanoma syndrome or FAMMM syndrome), *STK11* (Peutz-Jeghers syndrome), genes that cause Lynch syndrome (such as *MLH1* and *MSH2*).<sup>7, 8</sup> These HRI can be offered surveillance in formal multidisciplinary pancreatic cancer screening programs.<sup>4</sup>

It has been shown that some PDACs arise from well-defined precursor lesions such as microscopic pancreatic intraepithelial neoplasia (PanINs) or macroscopic intraductal papillary mucinous neoplasms (IPMNs)<sup>7, 9, 10</sup> and detection of high-risk PDAC precursors might be suitable targets for screening.<sup>4</sup> Consensus guidelines for the surveillance of HRI have been developed.<sup>4</sup> The goal of screening and surveillance of HRI is to detect early stage pancreatic cancer and high-grade dysplasia (HGD) in precursor lesions (IPMN and PanIN).

Little has been reported regarding the outcome of HRI who have undergone pancreatic resection for screening-detected lesions. A recent paper from our group evaluated risk factors for neoplastic progression among HRI in the CAPS program.<sup>5</sup> In this study, we report the outcomes after pancreatic surgery for screening-detected lesions.

## Methods

### Study Design

We analyzed prospectively collected data from the Cancer of the Pancreas Screening (CAPS) studies between 1998 and 2014<sup>11–13</sup> that consecutively enrolled HRI for one-time screening (CAPS 1–4) at The Johns Hopkins Hospital.<sup>11–13</sup> In this report, outcomes were tracked for HRI who continued surveillance at The Johns Hopkins Hospital. Outcomes reported in the current study were updated from enrollment to November 2017 by review of the electronic medical chart, mailed or emailed patient survey, telephone call by a study team member, and internet searches of obituaries and registered deaths. The study protocols were approved by the Institutional Review Board at the Johns Hopkins University (study ID NA\_00087754, NA\_00044490, and NA\_00005455).

### Study Population

HRIs were defined as those with any of the following conditions: (1) three or more affected blood relatives with PDAC, including at least two related by first-degree, and with at least one of the affected related to the at-risk relative by first degree, (2) at least two affected first-degree relatives with PDAC, (3) Peutz-Jeghers syndrome regardless of family history of PDAC, (4) deleterious germline *p16* (*CDKN2A*) gene mutation or familial atypical multiple mole melanoma syndrome with one affected first-degree relative, (5) deleterious germline *BRCA2* gene mutation with one affected first-degree relative, (6) deleterious germline *BRCA2* gene mutation with two affected family members (non-first-degree) with PDAC, (7) deleterious germline *PALB2* gene mutation with one affected first-degree relative, (8) deleterious germline *ATM* gene mutation, and/or (9) deleterious germline mismatch repair gene mutation, such as Lynch syndrome, with one affected first-degree relative.<sup>4</sup> Those with Peutz-Jeghers syndrome were screened starting at the age of 30 years.<sup>4</sup> Individuals at high risk based on their family history began screening at the age of 50 years.<sup>5</sup>

Exclusion criteria were (1) established or clinically suspected pancreatic cancer, (2) prior pancreas-specific imaging protocol performed in the past 3 years, (3) medically unable to have an endoscopy, CT, or MRI procedure, (4) advanced or end-stage medical disease, and (5) follow-up < 6 months from baseline screening at The Johns Hopkins CAPS program.

## Screening and Surveillance Methods

Endoscopic ultrasonography (EUS) was used for baseline screening from 1998 to 2002 (CAPS 1 study),<sup>12</sup> and pancreatic protocol computed tomography (CT) was added to EUS from 2002 to 2004 (CAPS 2 study).<sup>11</sup> In the CAPS 3 study, 216 subjects underwent one-time screening with EUS, CT, and magnetic resonance imaging (MRI) pancreatic protocol with cholangiopancreatography (MRCP).<sup>13</sup> Since 2005, surveillance of enrolled HRI was performed mainly with EUS and MRCP, given higher detection rates of small pancreatic lesions compared with computed tomography (CT) without repeated radiation exposure.<sup>4, 7, 9, 13</sup> CT was used if there was any solid pancreatic lesion, rapid cyst growth, or an indeterminate imaging abnormality such as benign-appearing cyst with mild main duct dilation detected by EUS or MRCP.

Highly experienced gastroenterologists (MC, EJS, and AML) performed sedated upper endoscopy followed by EUS imaging using an electronic radial and/or linear echoendoscope (Olympus Corporation, Center Valley, PA). Fine-needle aspiration was performed during the same sedation procedure as indicated by the presence of a pancreatic mass or mural nodule in a cyst, according to standard medical care guidelines, with on-site cytopathology review of specimens for adequate tissue acquisition. Highly experienced radiologists (I.K. and E.F.) interpreted MRI and CT results. Gadolinium-enhanced MRCP was used using a specific pancreas protocol. All MRI sequences were obtained at a minimum of 1.5 or 3.0 Tesla (GE, Waukesha, WI or Siemens, Malvern, PA) using a phased-array torso coil. Axial breath-hold unenhanced and dynamic contrast-enhanced (0.1 mmol/kg of body weight), T1-weighted, 3-dimensional, fat-suppressed, spoiled gradient-echo imaging were acquired in the arterial, portal venous, and delayed phases at 20 seconds, 70 seconds, and 3 min, respectively.

HRI with no pancreatic abnormalities at baseline were followed at 12-month intervals, typically alternating between EUS and MRI. HRI with a low-risk cyst without worrisome features (cyst size > 3 cm, mural nodules, thickened/enhancing cyst walls, main duct dilation 5–9 mm, abrupt change in duct caliber with distal atrophy, lymphadenopathy)<sup>14, 15</sup> or rapid cyst growth (defined as > 2 mm in 6 months or > 4 mm per year)<sup>5</sup> continued surveillance at 6–12 months. Those with an indeterminate solid lesion had follow-up screening at 3 months, if surgery was not imminent.

For those with a dilated pancreatic duct with or without a benign-appearing cyst, or main pancreatic duct stricture without a mass, repeat imaging was performed at 3 months.<sup>5</sup> Surveillance intervals were adjusted depending upon the stability of the indeterminate lesion and absence of radiologic features of neoplastic progression.<sup>5</sup>

HRI with a suspicious soft tissue lesion or discrete solid pancreatic mass were referred to a pancreatic surgeon. All patients with indeterminate lesions, masses, or cysts with worrisome features were discussed at regular scheduled multidisciplinary conference involving surgeons, radiologists, gastroenterologists, and pathologists.

Patients with planned total pancreatectomy or completion pancreatectomy saw a local endocrinologist and received counseling on glucose monitoring, diet, and postoperative diabetes management from a physician specializing in diabetes and diabetes nurse.

Pancreatic surgery at The Johns Hopkins Hospital was performed by highly experienced pancreatic surgeons (MW, CY, RS, JH, MM, and CW). Pathologic specimens were processed according to an established protocol involving careful examination of the frozen sections during surgery, the final gross specimen, and histologic sections obtained at a maximum of 1-cm intervals. One expert pathologist (R.H.) provided a pathologic diagnosis using a standard,<sup>10</sup> consensus international classification system and revised classification system from the Baltimore consensus meeting.<sup>16</sup>

To report surgical morbidity, we report the specific complications following pancreatic resection proposed by the International Study Group of Pancreatic Surgery in 2017.<sup>17</sup> Delayed gastric emptying (the inability to return to a standard diet by the end of the first postoperative week requiring prolonged nasogastric intubation) as well as postoperative pancreatic fistula (drain output of any measurable volume of fluid with an amylase level > 3 times the upper limit of institutional normal serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula).<sup>17</sup> Other postpancreatectomy complications included postpancreatectomy hemorrhage.<sup>17</sup> Other determined outcomes were overall mortality,<sup>18, 19</sup> morbidity, length of stay,<sup>20, 21</sup> and 30-day readmission and 90-day mortality.<sup>19</sup> We assessed the incidence of new-onset diabetes mellitus in those with partial pancreatic resection (either pancreaticoduodenectomy or distal pancreatectomy, without subsequent completion pancreatectomy), which was defined by the American Diabetes Association, to include (1) hemoglobin A1C  $\geq 6.5\%$ , (2) fasting plasma glucose  $\geq 126$  mg/dL, (3) 2-h plasma glucose  $\geq 200$  mg/dL during an oral glucose tolerance test, and/or (4) those with classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose  $\geq 200$  mg/dL.<sup>22</sup>

## Statistical Analyses

The chi-square, Fisher's exact test, and *t* test were performed for categorical and numeric variables, where appropriate, to compare outcomes. Two-tailed *p* values less than 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 14.1 (Stata Corporation, Dallas, TX) and JMP Pro 13.0 (SAS Institute Inc., Cary, NC) software packages.

## Results

### Baseline Patient Characteristics

From 584 HRIs enrolled in the CAPS 1–4 studies beginning in 1998, 123 HRIs were excluded because of <6-month follow-up and 104 were not included due to continued surveillance at other institutions. For the current study, 354 asymptomatic HRIs who continued surveillance at the Johns Hopkins Hospital with follow-up of more than 6 months after baseline screening were included. The mean follow-up time at study closure to November 2017 was 7.6 years (range 0.7–16.6 years). Among 48 HRI (mean age  $\pm$  SD  $69 \pm 10.5$  years, 27 males (56.3%)) who had screening-detected lesions and underwent pancreatic resections, 42 patients (87.5%) had first-degree relatives with PDAC, of which 30/42 patients (71.4%) also had second-degree relatives with PDAC. All patients were non-Hispanic white. There were 19/48 patients (39.6%) with history of cigarette smoking, and 6/48 (12.5%) had active smoking at the index screening. There were 6 patients (12.5%) with baseline diabetes, of which one patient was insulin dependent, prior to the index screening. Mean body mass index prior to index pancreatic resection was  $27.9 \pm 5.4$  kg/m<sup>2</sup>.

### Type and Number of Pancreatic Operations

Among 48 HRI who had screening-detected lesions and underwent pancreatic resections, 57 operations were performed (48 initial and 9-second surgery procedures) between November 1998 and January 2017. The type of the initial operation included pancreaticoduodenectomy (*n* = 16, 33.3%), distal pancreatectomy (*n* = 26, 54.2%), and total pancreatectomy (*n* = 6, 12.5%). Eight operations (16.7%) were minimally invasive (5 laparoscopic and two robotic-assisted distal pancreatectomy, 1 laparoscopic total pancreatectomy) (Table 1).

The first 16 operations performed between 1998 and 2007 were partial resections aimed at treating the detected lesion or the most concerning dominant lesion(s) in HRI with multiple pancreatic lesions. All 6 total pancreatectomies and 9

completion pancreatectomies were performed for multifocal and/or metachronous lesions beginning in March 2007.

Among 48 patients who underwent initial partial pancreatic resection, 9 patients (19%) that eventually had completion pancreatectomy (4 pancreaticoduodenectomy, 5 distal pancreatectomy) were operated for new lesions in the remnant gland detected at a median of 3.8 years. Six of these patients had new and/or enlarging cysts—1 BD-IPMN with HGD, 2 BD-IPMN with moderate-grade dysplasia, 3 with BD-IPMN with low-grade dysplasia but 1 HRI also had 10 synchronous PanIN-3 lesions. Three of the remaining 9 patients had second surgeries for new solid masses (1 HRI with a well-differentiated, grade 1, nonfunctional pancreatic neuroendocrine tumor (PanNET); 1 HRI with PanIN-2 with lobulocentric atrophy, and 1 HRI with PDAC detailed below). Another patient who initially had a Whipple for a well-differentiated T3N1M0 grade 1 PanNET presenting as an asymptomatic mass in the head at baseline screening developed a new 1 cm low-grade well-differentiated PanNET in the tail, which was resected at completion distal pancreatectomy 6 years after the index surgery (Table 1).

Two of the 48 patients (4%) under surveillance developed a metachronous PDAC in the remnant pancreas after initial surgery; both for benign IPMN. One of these patients with an incident PDAC underwent pancreaticoduodenectomy for BD-IPMN with low-grade dysplasia and developed a mass with distal atrophy and duct dilation in the body of the pancreas 7 years later while under surveillance. He delayed surgery for almost a year and final pathology showed a T3N0M0 PDAC. The second patient with a metachronous PDAC had Whipple procedure for a mixed IPMN with moderate dysplasia in a BD-IPMN and low-grade dysplasia in the main duct. He developed PDAC in the tail with the metastatic disease despite annual CT surveillance after his first surgery 5 years later. The PDAC presented with duct dilation and an indeterminate soft tissue lesion at the anastomosis.

### Nonoperable PDAC in HRI Without Prior Surgery

Three of the 354 screened HRI presented with unresectable and/or metastatic PDAC after their initial screening visit; all were either late or had stopped pancreas surveillance. One Ashkenazi Jewish patient with 2 affected first-degree relatives had a mildly dilated main pancreatic duct with mild features of chronic pancreatitis at baseline. He developed new subcentimeter pancreatic cysts in the tail and head of the pancreas. He was 2 years overdue for his annual surveillance imaging due to intervening medical problems, which in retrospect, were manifestations of a paraneoplastic syndrome (peripheral neuropathy, coagulopathy). He presented with a PDAC in the head with liver metastases.

The second patient underwent initial screening EUS, CT, and MRI as part of the CAPS 3 study. He tested negative for

**Table 1** Characteristics of 48 resected high-risk individuals and screening-detected lesions, stratified by the highest grade of pathologic diagnosis at end of follow-up period (including second operations)

Pathology (n)	Indication for surgery (n)	Median age (years)/% male	Type of operations (number of open/minimally invasive)	Median tumor size (cm)	AJCC stage for PDAC	Median follow-up (years)/% alive	Overall 1-year survival/5-year survival	Cause of death, where applicable (n)
PDAC (11)	Solid mass (8) Cyst with duct dilatation (1) Rapid cyst growth (2)	65/54.6%	Whipple (6/0) <sup>a</sup> Distal (3/0) Total (2/0)	2.7 (IQR 1.5–3.5)	Stage IA, T1N0M0 (2) Stage IIA, T3N0M0 (2) Stage IIB, T2N1M0 (4) Stage IIB, T3N1M0 (2) Stage IV, T3N1M1 after remote Whipple (1) <sup>a</sup>	4.7/45.6%	90%/60%	PDAC-related (4), non-PDAC related (2)
High-grade PDAC precursors (10) IPMN HGD (6) <sup>c</sup>	Mass (1) Cyst with mural nodule (1) Cyst with main duct dilatation and mural nodules (1)	66/ 16.7%	Whipple (2/0) Distal (3/1)	1.6 (IQR 1.0–2.3)	Tis (including 2 combined IPMN)	7.4/100%	100%/100%	No death
PanIN-3 (4)	Rapid cyst growth (3) Cyst with main duct dilatation (1) Main PD stricture with dilation, no mass (1) Rapid cyst growth, multifocal cysts (2)	66/ 0%	Whipple (2/0) <sup>b</sup> Total (2/0)	1.2 (IQR 0.9–1.5)	Tis (including 1 main duct PanIN3)	7.6/85.7%	100%/100%	Non-PDAC related (1) at 7 years
Low-grade PDAC precursors (24): PanIN2, IPMN-LGD, IPMN-MGD	Mass (10) Cyst with duct dilatation (4) Rapid cyst growth (10)	62/ 56%	Whipple (5/0) Distal (12/5) Total (1/1)	1.6 (IQR 0.7–2.2)	N/A	8.4/96%	100%/100%	Non-PDAC related (1) at 11.2 years
Pancreatic neuroendocrine tumor > 5 mm (4)	Mass with positive EUS-FNA cytology (4)	51/100%	Whipple (2/0) <sup>e</sup> Distal (1/1) Total (0/0)	1.2 (IQR 1–1.8)	Stage IIB, T3N1M0 (1) Stage IA (3)	8.4/100%	100%/100%	No death

<sup>a</sup> Patient had a Whipple operation for a BD-IPMN with moderate dysplasia in the head, with main duct involvement (mild dysplasia) at the margin, and presented 5 years later with a metachronous unresectable pancreatic tail PDAC with liver metastases despite annual CT surveillance. Given no pancreatic resection at the time of PDAC diagnosis due to metastatic stage, this patient was excluded from further analyses

<sup>b</sup> IPMN HGD and PanIN3 at completion pancreatotomy after initial resection

<sup>c</sup> Patient had a Whipple procedure for a pT3N1b NET, then developed a new pT1N0 PanNET in the remnant pancreatic tail, requiring completion distal pancreatotomy

germline mutations in the *BRCA1* and *BRCA2* genes and stopped surveillance. Seven years later, he presented with symptomatic unresectable PDAC and opted for palliative care. He tested positive for a germline *PALB2* gene mutation.

A third patient had a *BRCA2* mutation who had been diagnosed with stage 3 ovarian cancer with a baseline screening CT, developed a subcentimeter cyst in the head of the pancreas 1 year later. She was advised to have surgery for rapid enlargement of the cyst after a 3-month follow-up EUS. She declined surgery. Unfortunately, she developed a symptomatic primary PDAC in the head of the pancreas with liver metastases 21 months after her initial visit.

### Surgical Outcomes: Length of Stay, Operative Morbidity, and Mortality

The median length of stay for pancreatic resection was 7 days (IQR 5–11). Those receiving total pancreatectomy required longer length of stay (median 11.5 days, IQR 8.5–13.3) compared with those received Whipple operation or distal pancreatectomy ( $p = 0.0009$ , Table 2). There were 10 patients in this cohort with screening-detected PDAC who underwent pancreatic resection(s), of which 9 patients (90%) achieved negative margin (R0) resection. The tenth patient with resectable PDAC had a microscopic positive margin (Whipple).

Overall, postpancreatectomy complications developed in 17 of 48 patients (35.4%) (Table 2). Patients receiving Whipple operation at initial surgery had more complications (10/16, 62.5%) compared with other groups ( $p = 0.02$ ), particularly delayed gastric emptying (6/16, 37.5%,  $p = 0.01$ ). Other

complications such as surgical site infection, anastomotic leak, and cholangitis were comparable among partial and total pancreatectomy groups (Table 2). Length of stay was longest in total pancreatectomy patients. Weight loss was lowest in distal pancreatectomy patients compared with pancreaticoduodenectomy and total pancreatectomy patients. Minimally invasive pancreatic resection was not associated with improved outcomes compared with open pancreatic resection in this cohort.

There were 3 hospital readmissions within 30 days (6.2%). These included an intra-abdominal abscess on postoperative day 10 requiring a 12-day hospitalization and percutaneous drainage, dehydration on postoperative day 18 requiring a 3-day hospitalization, and admission for delayed gastric emptying on postoperative day 28 initially requiring total parenteral nutrition followed by percutaneous endoscopic gastrostomy. There was no 90-day mortality or intra-abdominal hemorrhage.

### Postoperative Diabetes Mellitus

Six patients had diabetes at baseline screening (1 type 1 diabetes, 5 type 2 diabetes). There were 30 patients without diabetes mellitus prior to surgery who had partial pancreatic resection. Six of these patients (20%) developed diabetes, with no difference in those who had a Whipple procedure (20%) versus distal pancreatectomy (20%) (Table 2). One of the 6 patients who underwent total pancreatectomy had prior history of diabetes. Preoperative obesity, defined as a body mass

**Table 2** Postoperative complications after pancreatic resection for screening-detected lesions, stratified by initial type of resection (per patient analysis)

Variables	Whipple ( $N = 16$ )	Distal pancreatectomy ( $N = 26$ )	Total pancreatectomy ( $N = 6$ )	$p$ value
Follow-up time (years, median, IQR)	7.3 (3.9–11.8)	7.4 (4.3–10.4)	7.6 (2.3–11)	1.00
Length of stay (days, median, IQR)	7 (6.8–14.3)	6 (5–7)	11.5 (8.5–13.3)	0.0009
Overall complications ( $n$ , %)	10 (62.5%)	5 (19.2%)	2 (33%)	0.02
Delayed gastric emptying ( $n$ , %)	6 (37%)	1 (3.9%)	2 (33%)	0.01
Grade A pancreatic fistula and anastomotic leak ( $n$ , %)	0	1 (3.9%)	0	0.64
Grade B pancreatic fistula and anastomotic leak ( $n$ , %)	2 (12.5%)	2 (7.7%)	0	0.50
Grade C pancreatic fistula and anastomotic leak ( $n$ , %)	0	0	0	–
Surgical site infection ( $n$ , %)	2 (12.5%)	2 (7.7%)	0	0.50
Cholangitis ( $n$ , %)	2 (12.5%)	1 (3.9%)	0	0.38
30-day readmission ( $n$ , %)	2 (12.5%)	1 (3.9%)	0	0.38
Postoperative new onset diabetes ( $n$ , %) <sup>a</sup>	2/10 (20%)	4/20 (20%)	6/6 (100%)	1.00
Diarrhea	4 (25%)	3 (11.5%)	4 (67%)	0.02
Steatorrhea	3 (18.8%)	3 (11.5%)	4 (66.7%)	0.02
Weight loss > 10 lbs	12 (75%)	9 (34.6%)	5 (83.3%)	0.01
Weight gain	1 (6.3%)	2 (7.7%)	0	0.65
Pancreatic enzyme replacement therapy	9 (56.3%)	9 (34.6%)	5 (83.3%)	0.06

<sup>a</sup> High-risk individuals without baseline diabetes mellitus who underwent partial pancreatic resections without completion total pancreatectomy

index of 30 kg/m<sup>2</sup> or higher, was not associated with new-onset diabetes (odds ratio 7.2, 95% CI 0.58–175.3,  $p = 0.12$ ).

Among 48 HRI who had pancreatic resections, 10 patients (21%) received an insulin pump after pancreatic resection. One of these patients (10%) had partial pancreatic resections. Patients with diabetes at baseline prior to pancreatic resection were more likely to be managed with an insulin pump post-operatively compared with those without preexisting diabetes (4/6 (67%) versus 6/42 (14%) patients, respectively,  $p = 0.01$ ). Two of the 15 (13%) patients with eventual complete pancreatectomy (6 initial total pancreatectomy plus 9 with completion pancreatectomy) developed severe dysglycemia requiring an emergency department visit, including one who required a hospitalization. However, no severe hypoglycemic complications (syncope, seizure, death) occurred in any patient.

### Pathologic and Oncologic Outcomes According to Surgical Indication

The final diagnoses, indication for surgery, survival, and cause of death for these patients are summarized in Table 1. Twenty-two HRI underwent surgery for detected solid pancreatic masses. Four of these HRI who had surgery for a pancreatic mass had a PanNET without evidence of PDAC or PanIN-3 (Table 1). All 4 PanNET were confirmed preoperatively by EUS-guided fine needle aspiration. Of the remaining 9 surgical patients who developed solid pancreatic masses during surveillance, 8 were proven to be PDAC and 1 was an IPMN with HGD.

Three patients with pancreatic cysts (1 with associated duct dilation, and the two other with rapid cyst growth) developed PDAC (Table 1). Five HRI with cysts with at least one worrisome feature according to the International Consensus Guidelines (specifically, mural nodule (1), main duct dilation with mural nodules (1), rapid growth (3)) were proven to have IPMN with HGD. In 4 patients who had surgery for a pancreatic cyst with main duct dilation (1) or rapid growth plus multifocal cysts (2), incidental PanIN-3 was found in the resected pancreas along with benign branch duct IPMN. One duct stricture without a mass proved to be an unusual isolated PanIN-3 in the main duct.

The remaining 24 HRI presenting with indeterminate small solid masses (10) or cysts with worrisome features (14) had only low or moderate grade precursor lesions (Table 1).

There were no significant differences in the proportion of PDAC and tumors with HGD resected during the early, middle, and later study periods, 6/15 (40%) between 1998 and 2006; 6/17 (35%) between 2006 and 2010; and 8/16 (50%) from 2010 to 2017 ( $p = 0.68$ ).

In summary, 11 PDAC and 10 PDAC high-grade precursor neoplasms (6% of the 354 cohort) were detected during surveillance and surgically treated during the 19-year study period. The final pathological staging for the 10 resected PDAC

patients is detailed in Table 1, including two stage I and eight stage II cancers. Seven of the 10 HRI with resected PDACs received adjuvant chemoradiation therapy. Importantly, the overall mortality and disease-specific mortality for operated PDAC detected during 19-year study period were 60% and 40%, respectively. Two of the resected PDAC patients died of non-PDAC causes. One patient survived 12 years after surgery but died of complications from surgery for an incident gastric cancer. The other PDAC survivor with stable recurrent disease died from complications after a motor vehicle accident 2 years after his total pancreatectomy.

The 1-year overall survival was 90% and 5-year overall survival of 60% for PDAC patients (Table 1). All but two of the 34 HRI that underwent resection for with pancreatic precursor lesions were alive at study end. The 2 deceased HRI with benign precursors died of non-PDAC causes at 7 and 11 years after surgery.

### Discussion

The CAPS cohort (consisting of HRI enrolled in the CAPS 1–4 studies) is the largest single center cohort of individuals at high risk for pancreatic cancer with the longest follow-up (19 years) to date. We recently reported the incidence, rate, and risk factors for neoplastic progression to PDAC or IPMN-HGD/PanIN3 after baseline screening in this long-term cohort.<sup>5</sup> We found that the majority (93%) of progressors (neoplastic progression was defined by the development of pathologically proven PDAC and/or IPMN-HGD/PanIN3, radiologic progression was defined as the development of a lesion with one or more worrisome features after baseline imaging)<sup>5</sup> had lesions with worrisome features prior to their diagnosis (solid mass, dilated main pancreatic duct, abrupt change in duct caliber, and rapid cyst growth > 4 mm/year) that were detectable by EUS, MRI, and/or CT. We also noted the presence of multiple cysts (> 3) at baseline was a significant risk factor for neoplastic progression, which occurred at an average age of 67 years. The median time from baseline to PDAC diagnosis of 4.8 years (interquartile range 1.6–6.9 years).<sup>5</sup>

The current study focuses on the outcomes of operated HRI. The overall postoperative complication rate was 35% with zero 90-day mortality, which compares favorably with previously published data regarding complications and death after pancreatic resection of 30–60%<sup>18</sup> and 1.89%<sup>17</sup> to 7.4%,<sup>18</sup> respectively. In this study, we used the definitions of delayed gastric emptying, pancreatic fistula, and pancreatic hemorrhage following those proposed by the International Study Group of Pancreatic Surgery.<sup>17</sup> The complications found in this cohort were comparable with prior published data using the same definitions, including 14.6–24.2% risk of delayed gastric emptying<sup>23</sup> and 12% risk of grade B

pancreatic fistula.<sup>24</sup> There was no intra-abdominal hemorrhage in our cohort; prior prospective studies have reported postpancreatectomy hemorrhage rates as high as 5.7%.<sup>25</sup> Other surgical-related outcomes, without established definitions by the International Study Group of Pancreatic Surgery, remained low, including surgical site infection as well as cholangitis.

With regard to index length of stay, our HRI treated with pancreaticoduodenectomy had relatively shorter average length of stay of 7 days, compared with that reported in a recent analysis of pancreaticoduodenectomy procedures in the ACS-NSQIP targeted pancreatectomy database (length of stay 10–11 days).<sup>20</sup> The index length of stay in our CAPS cohort that underwent distal pancreatectomy (6 days) was comparable with that reported in large Norwegian database including 546 distal pancreatic resections (length of stay 7 days).<sup>21</sup> Furthermore, the 30-day readmission rate (3/48 patients, 6.2%) in our CAPS cohort was lower than that reported in recently published surgical series (13.9–19.1%).<sup>20, 21</sup>

The incidence rates of postoperative diabetes from this series (20% after Whipple, 20% after distal resection) are comparable with those noted in prior published studies reporting 18% and 29% of patients who underwent pancreaticoduodenectomy and distal pancreatectomy, respectively.<sup>26</sup> However, recent data suggest a lower incidence of diabetes after pancreatic surgery than previously reported. In patients treated with a Whipple procedure, the incidence of postoperative diabetes was 10.6% in a large multicenter prospective study and 14.5% in a systematic review and meta-analysis.<sup>27</sup> A systematic review showed that 14% of patients developed new-onset diabetes after distal pancreatectomy.<sup>28</sup> Our relatively higher rates of new-onset diabetes compared with more recent data might be related to the presence of lobulocentric atrophy and chronic pancreatitis associated with PanIN,<sup>29</sup> the small study sample size, and the accumulating risk for diabetes in older patients.<sup>30</sup>

Prophylactic pancreatectomy is not recommended as the operative approach for HRI.<sup>4</sup> Only 20 of 48 (42%) HRI who underwent partial pancreatectomy had PDAC or high-grade precursors in their resected pancreata; these are the main targets for screening defined by the International CAPS Consortium.<sup>4</sup> The remaining HRI (58%) had lower-grade neoplasms, which one could argue did not, in hindsight, require surgery. Many of these pancreatic resections occurred in the earlier years of the CAPS program when the indications for surgery included resection of lower grade neoplasms.<sup>11</sup> Selection of HRI for surgery remains challenging. When a solid mass is detected in a HRI, surgery is indicated in an operable patient, regardless of the EUS-guided cytological diagnosis. False positive and false negative cytology results have

been reported in several pancreatic screening studies.<sup>6, 11–13, 31</sup> Furthermore, the management of detected cystic lesions in HRI is even more difficult, particularly when the patient is healthy and asymptomatic. Pancreatic cysts are the most common imaging abnormality in HRI and the majority are low-risk BD-IPMNs.<sup>4, 13</sup> The worrisome features and high-risk stigmata previously described to aid in the management of sporadic mucinous cysts<sup>14, 15</sup> are not sufficiently specific for PDAC or precursors with HGD. Their absence also does not assure us of the absence of malignancy.<sup>11–13, 31–34</sup> Hence, the data from our CAPS studies<sup>5, 11–13</sup> and other surveillance studies<sup>6, 31–36</sup> suggest that pancreatic imaging is insufficient for the optimal selection of patients for surgery. Early detection and prevention of PDAC could be improved by the discovery and validation of biomarkers in cyst fluid,<sup>37, 38</sup> juice,<sup>39–41</sup> and blood<sup>42–44</sup> that may minimize unnecessary surgery for low-risk tumors.

Some limitations of our study should be considered. First, the CAPS studies were conducted in an academic tertiary referral center with highly skilled endoscopists, pancreatic surgeons, radiologists, and pathologists, limiting generalizability of pancreatic surgery outside a specialized center with a multidisciplinary surveillance program. Second, the current study only reports the outcomes from patients diagnosed and followed at one hospital. Third, the proportion of patients in our CAPS cohort that underwent pancreatic surgery was small precluding more extensive evaluation of surgical management. Fourth, practice has evolved over the study period, with improved understanding, and better imaging technology. The indications for surgical resection have evolved over time but remain individualized tailored to estimated cancer risk based on lesion characteristics by imaging, estimated cancer risk based on age, inherited/familial risk factors, and patient preferences. Finally, the CAPS study HRI are a highly motivated, relatively healthy group of patients that may have better outcomes that are not representative of other patients.

In conclusion, pancreatic resection for screening-detected lesions in HRI was associated with reasonable morbidity, relatively short length of stay and low readmission rate, no 90-day mortality, and significant survival compared with the national data on sporadic pancreatic cancer.

**Acknowledgments** CAPS 3 study participating centers and co-investigators (listed in alphabetical order) Dana Farber Cancer Institute, Boston, MA (Koenraad Morteale, John Saltzman, Sapna Syngal); The Mayo Clinic, Rochester, MN (Joel Fletcher, Gloria Petersen, Naoki Takahashi, Mark Topazian), MD Anderson Cancer Center, Houston, TX (Priya Bosale, Jeffrey Lee, Eric Tamm, Raghunandan Vikram), and University of California, Los Angeles, CA (James Farrell, Daniel Margolis).



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Study support: Marcia Canto and Michael Goggins.

Obtained funding: Marcia Canto, Ralph Hruban, and Michael Goggins.

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**Funding** This work was supported by the National Institutes of Health grants (CA210170, CA176828, CA62924, CA154823, CA132829), Susan Wojcicki and Dennis Troper, the Pancreatic Cancer Action Network, the Lustgarten Foundation for Pancreatic Cancer Research, the Rolfe Pancreatic Cancer Foundation, the John and Peter Hooven Memorial Endowment, Hugh and Rachel Victor, and ChiRhoCin, Inc.

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