

Surveillance for pancreatic cancer in high-risk individuals

Running title: Outcomes of pancreatic cancer surveillance

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Abbreviations:

APC, adenomatous polyposis coli; ATM, ataxia telangiectasia mutated; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FAMMM, familial atypical multiple mole melanoma syndrome; FDR, first degree relative; HBOC, hereditary breast and ovarian cancer; HRI, high-risk individuals; HRN, high-risk neoplastic precursor lesion; IPMN, intraductal papillary mucinous neoplasm; MMR, mismatch repair genes; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasia; PanNET, pancreatic neuroendocrine tumour; PDAC, pancreatic ductal adenocarcinoma; SDR, second degree relative.

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Keywords: pancreatic cancer; surveillance; pancreas; pancreatic tumours; pancreatic surgery; outcome; survival

ABSTRACT

Background

Surveillance of high-risk individuals for pancreatic ductal adenocarcinoma (PDAC) and its precursors might lead to better outcomes. The aim of this study was to determine prevalence and outcomes of PDAC and high-risk neoplastic precursor lesions among such patients participating in surveillance programmes.

Method

A multicentre study was conducted through the International CAPS Consortium Registry to identify high risk individuals who had undergone pancreatic resection or progressed to advanced PDAC while under surveillance. High-risk neoplastic precursor lesions were defined as: pancreatic intraepithelial neoplasia 3 (PanIN-3), intraductal papillary mucinous neoplasia (IPMN) with high-grade dysplasia and pancreatic neuroendocrine tumours (PanNET) equal to or greater than 2 cm in diameter.

Results

Of 76 high risk individuals identified in 11 surveillance programmes; 71 had undergone surgery and 5 had been diagnosed with inoperable PDAC. Of the 71 resections 32 (45%) had PDAC or a high-risk precursor (19 PDAC, 4 main duct IPMN, 4 branch duct IPMN, 5 PanIN-3; the other 39 patients had lesions thought to be associated with lower risks of neoplastic progression. Age ≥ 65 , female gender, carriage of a gene mutation and location of a lesion in the head/uncinate region were associated with high-risk precursor lesions or PDAC. The survival of high risk individuals with low-risk neoplastic lesions versus those with high-risk precursor lesions did not differ. Survival was worse among patients with PDAC. There was no surgery-related mortality.

Conclusion

A high proportion of high risk individuals who underwent surgical resection for screen or surveillance-detected pancreatic lesions had a high risk neoplastic precursor lesion or PDAC at the time of surgery. Survival was better in high risk individuals who had either low or high-risk neoplastic precursor lesions compared to those who had developed PDAC.

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INTRODUCTION

Despite improvements in treatments for PDAC, it remains the third leading cause of cancer deaths in the United States (U.S.) with a 5-year survival of only 8%¹. By 2030, PDAC is projected to become the second leading cause of cancer-related death in that country.² Advances in screening, prevention, and treatment have the potential to change pancreatic cancer incidence and death rates². Inherited susceptibility is thought to be a major factor in the development of PDAC, accounting for 5-10% of cases³. Surveillance for PDAC and its precursor lesions in asymptomatic high-risk individuals is increasingly being performed worldwide⁴⁻¹⁵. These high-risk individuals can be categorized into two groups: carriers of known PDAC-associated gene mutations (especially carriers of deleterious mutations in *CKDN2A*, *BRCA2*, *BRCA1*, *ATM*, *TP53*, *PRSS1* or *STK11*), and first-degree relatives in familial PDAC (clustering of at least two first-degree blood relatives with PDAC)¹⁶. The goals of surveillance have been previously described by the CAncer of the Pancreas Screening (CAPS) Consortium¹⁷. These include the detection and treatment of early invasive pancreatic cancer (T1N0M0) at baseline or follow-up; detection and treatment of any invasive resectable cancer at baseline screening; detection and treatment of multifocal pancreatic intraepithelial neoplasia 3 (PanIN-3); and the detection and treatment of intraductal papillary mucinous neoplasia (IPMN) with high-grade dysplasia.

Few studies have described the surgical pathology findings in high-risk patients who have undergone surgery^{15,18}. The CAPS Consortium Registry was created to gather information rapidly about the experience of surveillance. In this study, we evaluated the diagnostic yield and outcomes of high-risk individuals who underwent surgical resection or progressed to invasive cancer and examined the characteristics of patients who developed high-risk neoplastic precursor lesions or PDAC.

METHODS

All participating centres in the CAPS Consortium (36 centres, 9 countries) were requested to enter patient information data for high-risk individuals participating in their PDAC-surveillance programmes who had either undergone pancreatic surgery because of the detection of a suspicious pancreatic lesion, or who had progressed to advanced non-resectable malignant disease. Data were collected through the use of web-based software (OmniComm™ Electronic Data Capture). Anonymized clinical and demographic information was collected relating to gender, age, tobacco and alcohol use, diabetes mellitus, history of pancreatitis, body mass index (BMI), known gene mutations, and family history of PDAC. In addition, pancreatic imaging modalities that detected the lesions, characteristics of the lesions detected by imaging, timing of detection, therapy, pathology and outcomes after surgery or diagnosis of advanced PDAC were also recorded. Research protocols of all participating centres were largely based on the consensus statements of the Cancer of the Pancreas Screening (CAPS) Consortium produced in 2013¹⁷, acknowledging that the nature of this study and its time span made it inevitable that differences between protocols of screening centres would exist.. The index examinations and follow-up examinations were carried out using MRI and/or endoscopic ultrasonography. However, when suspect lesions were detected, other modalities, such as CT imaging, were often used for further characterization and staging. All individuals in this study provided written informed consent for their participation in the respective PDAC surveillance programmes as approved by the Ethical Committees of the participating centres and the study was conducted in accordance with the Declaration of Helsinki.

Participants with pathologically proven high-risk neoplastic precursor lesions or pathologically proven PDAC were compared to participants who underwent surgery but in whom the resection specimen harboured no high-risk precursor lesion or PDAC. HRN were defined as uni- or multifocal PanIN-3 lesions, main and branch-duct duct IPMNs with high-grade dysplasia and PanNETs ≥ 2 cm^{19 20}.

Statistical methods

Descriptive statistics were used to characterize patient and lesion characteristics. Univariable analyses (Chi square, or Fisher's exact test where indicated) were performed on possible risk factors associated with PDAC or high-risk neoplasia precursor lesions. All variables with a *P*-value < 0.200 in the univariable analyses were included in the multivariable analysis. Survival comparisons for different subgroups were plotted as Kaplan-Meier curves and hazard ratios calculated using Log Rank. All analyses were conducted using the Statistical Package for the Social Sciences (V.21, SPSS Institute, Chicago, Illinois, USA).

RESULTS

Patient characteristics

A total of 76 high risk individuals were included from 11 PDAC-surveillance programmes in 4 countries (United States, The Netherlands, Israel, Italy). Between the 11 centres, some 1700 patients considered to be at high-risk underwent surveillance, of whom approximately 70% were female, Of the 76 included with precursor lesions, 5 were diagnosed with advanced disease during surveillance and 71

underwent surgery for a suspected lesion of whom two were discovered to have inoperable disease.

Baseline characteristics of all 76 high-risk individuals are summarized in Table 1.

High-risk neoplastic precursor lesions and (advanced) pancreatic ductal adenocarcinoma

High-risk neoplastic precursor lesions or PDAC were present in the surgical specimens of 32 (45%) of the 71 patients who underwent surgery. Among these, five (7%) patients had PanIN-3 lesions as the highest grade neoplastic lesion, four (6%) a branch-duct IPMN with high-grade dysplasia, four (6%) a main-duct IPMN, and 19 (27%) had PDAC. Pathology findings in all 71 high risk individuals who underwent surgery are summarized in Table 2, as well as lesion characteristics and type of surgery.

In 39 high-risk individuals, (55%) the indication for surgery was detected at their baseline screening evaluation. Of the remaining 32 (45%) patients, lesions were detected at follow-up investigations. In 9 of these 32 patients, a lesion was already present at previous investigations, for a mean time of 9 months prior to resection. These lesions initially did not meet resection criteria, but a changing appearance with time led to resection. In 10 of these 32 patients, there were mean delays of 7 months from their recommended screening interval (recommended screening intervals ranged from 3-24 months, depending on visualization and type of lesion). EUS detected the vast majority of lesions (87.3%). A total of 93 suspicious lesions were detected in the 71 patients who underwent surgery, of which 44 (47%) were cystic and 33 (36%) solid in appearance. Mean size of these 93 lesions was 14 mm, ranging between 3 to 51 mm.

Distal pancreatectomy was performed in 36 patients (51%) and a pancreaticoduodenectomy in 18 (25%). Complications of surgery were seen in 34 (48%) patients. The most common complications

were infection (14%), delayed gastric emptying (9%) and pancreatic fistula (6%). There were no surveillance or surgery-related deaths.

Of the five patients diagnosed with advanced disease during surveillance, three (60%) were identified at follow-up, the other two were detected at baseline evaluation.

Outcomes

The outcomes of both risk groups are summarized in Table 3. Of all 76 included patients, 61 (80%) are still alive, a mean 52 months after surgery or diagnosis of PDAC. Of 71 (83%) high risk individuals who underwent surgery 59 are still alive after surgery after a mean follow up of 54 months. Of the 12 patients who have died, 8 deaths were PDAC-related. Survival was significantly poorer for individuals with advanced PDAC as compared to the individuals who underwent surgery (survival 40% vs 83%, $P=0.05$; mean 10 vs 54 months, $P < 0.001$). Only 2 (3%) of 71 high risk patients who underwent surgery died within a year (all-cause 1-year mortality), compared to 2 of 5 with advanced PDAC; 52% survived more than 3 years after surgery.

Risk factors

Univariable analyses for factors associated with high-risk neoplastic precursor lesions or PDAC in the resection specimen (see Table 4) included age ≥ 65 at the time of surgery (OR 4.1, $P = 0.007$) and female gender (OR 3.8, $P = 0.007$). In the multivariable analysis, four factors were significantly associated with the presence of a high-risk precursor lesion or PDAC in the pancreatic resection specimen: age ≥ 65 at the time of surgery (OR 7.5, $P = 0.010$), female gender (OR 5.8, $P = 0.017$), carriage of a deleterious

mutation in a known pancreatic cancer susceptibility gene (OR 4.9, $P = 0.040$) and location of a lesion in the head/uncinate region of the pancreas (OR 4.2, $P = 0.041$).

Survival analysis

The pancreatic neoplasia grade was significantly associated with overall survival in high-risk individuals. Figure 1 shows the Kaplan-Meier curve for different pathologic subgroups. High-risk individuals with no or low-risk neoplastic lesions (group A, 39) and high-risk individuals with high-risk neoplastic precursor lesions (group B, 13) had the best survival, followed by those with stage I or II PDAC (group C, 16), and those with stage III or IV PDAC (group D, 8). The hazard ratio for group B compared to group A was 4.5 ($P = 0.163$), compared to group C, 13.1 ($P = <0.001$), and compared to group D, 25.3 ($P = <0.001$).

DISCUSSION

In this multicentre international study, high-risk neoplastic lesions or PDAC were present in 45% of the high-risk population that underwent surgery in a PDAC-surveillance programme. Survival between high-risk patients with no or low-risk lesions versus those with high-risk neoplastic precursor lesions- did not differ significantly. The patients who developed PDAC had a significantly higher overall mortality and poorer survival compared to those with no or low-risk neoplastic lesions.

Surveillance of high-risk individuals has the potential to improve the poor survival of PDAC and is increasingly being undertaken. In 2010, the CAPS Consortium was formed to help organize global

pancreatic surveillance. By pooling data from participating centres, important research questions pertaining to pancreatic surveillance can be assessed readily. The present analysis reports the pooled data of high-risk individuals for whom surveillance led to the detection of advanced disease or a lesion for which pancreatic surgery was performed.

Goals of surveillance previously described by the CAPS Consortium¹⁷ were early invasive cancers (T1N0M0), PanIN-3, main duct IPMNs and branch duct IPMNs with high-grade dysplasia. While PanNETs ≥ 2 cm were also included in the definition no such large PanNETs were detected. Timing of intervention is an important issue. In this series, 55% of the resection specimens harboured no high-risk neoplastic precursor lesion or PDAC, but did contain, for example, low-risk PanIN lesions (PanIN-1 or 2) or small PanNETs. Only long-term follow-up will disclose whether patients with resected low-risk lesions might have a reduced risk of subsequently developing PDAC. For some patients, surgical resection was performed too late, as only 3 of the 19 PDACs were T1. The main challenge in any surveillance programme is how to distinguish between those individuals that can be safely monitored and those who require surgery to resect a neoplastic lesion at a curable stage.

In this study, 55% of lesions that prompted surgery were detected at a baseline visit. This could raise the question whether one-time screening of high-risk individuals at a given age is also effective. Alternatively, when an advanced lesion is found at the index investigation, it could be argued that this lesion might have been detected at an earlier stage with potentially a better outcome if surveillance had started at an earlier age. As new lesions were detected in several patients who missed their follow-up visit by only a few months, it seems appropriate to adhere to an annual surveillance protocol, until more data are available from large prospective cohorts.

Although not all patients with main-duct IPMN progress to cancer, the overall 10-year risk is estimated at approximately 25%²¹. Only 2 patients in the present study were identified with these lesions prior to surgery. After pathological evaluation of the resection specimen 4 cystic lesions were reclassified as main-duct IPMN. Discrepancy between imaging and pathology is not an uncommon finding in this situation²².

The present study also sought to identify looked for risk factors that can easily be assessed preoperatively for association with high-risk neoplastic precursor lesions or PDAC in the resection specimens. Multivariable analyses showed age ≥ 65 , female gender, carriage of a gene mutation and location of a lesion in the head/uncinate region of the pancreas to be associated with the detection of a high-risk precursor lesion or PDAC in the resection specimen. Among female carriers of a gene mutation aged above 65 with a lesion suspicious for malignancy in the head/uncinate region of the pancreas, one should carefully weigh the option of pancreatic surgery versus continuing surveillance.

Survival analysis indicated that this was strongly influenced by the stage of disease at diagnosis²³. Importantly, the survival of patients with high-risk neoplastic precursors in their resection specimen was equal to those with no or low-risk neoplastic lesions, emphasizing the need to reliably identify high-risk precursor lesions more than early cancers.

The strength of this study is the international pooling of data on PDAC-surveillance programmes. This yielded a unique and sizeable cohort of high-risk patients participating in PDAC-surveillance programmes in whom either a suspicious lesion was detected for which they underwent surgery, or in whom an inoperable pancreatic cancer developed. The main limitations of this study are its design and

potential lead-time and length bias²⁴. Another limitation is that differences between protocols of the centres existed, particularly before publication of consensus statements of the Cancer of the Pancreas Screening (CAPS) Consortium in 2013¹⁷. Although this is the largest cohort described, its sample size is still too limited to assess differences in survival between R0 and R1 resections. Another limitation is the lack of detailed information of all 1700 high-risk individuals who underwent surveillance. Attention was specifically focused on the highly selected group who either developed advanced neoplasia or underwent pancreatic surgery and this study has added new, interesting and valuable data to the literature that provides some rationale to screening individuals at high risk for pancreatic cancer. More research is needed to better understand the risk factors for individuals at high risk of developing PDAC, and improve the selection of high-risk individuals for surgery. Collaborating internationally in large worldwide prospective studies seems the logical way forward.

Table 1. Baseline characteristics of all high-risk individuals who underwent surgery due to the detection of a suspicious pancreatic lesion or who were diagnosed with advanced pancreatic cancer during participation in PDAC surveillance.

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Age at surgery or diagnosis of advanced PDAC, mean (median, range, SD)	60.3 (59.8, 36-80, 11.6)	70.5 (65-80, 6.6)
Gender, male	37 (52.1%)	1 (20.0%)
Race		
White	67 (94.4%)	5 (100.0%)
Black	3 (4.2%)	-
Other	1 (1.4%)	-
Genetic background		
Familial pancreatic cancer (FPC)	52 (73.2%)	4 (80.0%)
CDKN2A (FAMMM syndrome)	7 (9.9%)	-
BRCA2 (HBOC)	3 (4.2%)	-
Peutz-Jeghers syndrome	3 (4.2%)	1 (20.0%)
BRCA1 (HBOC)	1 (1.4%)	-
TP53 (Li Fraumeni syndrome)	1 (1.4%)	-
MMR (Lynch syndrome)	1 (1.4%)	-
APC	1 (1.4%)	-
ATM	1 (1.4%)	-
PRRS1 (hereditary pancreatitis)	1 (1.4%)	-
Number of FDR with PDAC, mean (median, range, SD)	1.5 (1.0, 0-3, 0.8)	1.4 (0-2, 0.9)
Number of SDR with PDAC, mean (median, range, SD)	1.1 (1.0, 0-4, 1.0)	0.3 (0-1, 0.6)
Youngest family member affected by PDAC, mean (range, SD)	55.5 (33-77, 10.8)	63.3 (52-68, 7.5)
Body mass index, mean (median, range, SD)	27.3 (26.6, 18-48, 5.1)	26.1 (23-31, 3.7)
Personal history of diabetes	11 (15.5%)	2 (40.0%)
Number of months of diabetes prior to surgery or diagnosis of advanced PDAC, mean (median, range, SD)	36.6 (45.0, 0-63, 23.7)	66 (12-120, 76.4)
Personal history of pancreatitis	9 (12.7%)	1 (20.0%)
Smoking behavior		
Never smoker	46 (64.8%)	3 (60.0%)
Former smoker	20 (28.2%)	2 (40.0%)
Current smoker	3 (4.2%)	-
No data	2 (2.8%)	-
≥ 10 pack years in total	11 (15.5%)	1 (20.0%)
≥ 20 pack years in total	4 (5.6%)	-
Alcohol consumption		
Never consumer	38 (53.5%)	2 (40.0%)
Former consumer	12 (16.9%)	1 (20.0%)
Current consumer	19 (26.8%)	2 (40.0%)

No data	2 (2.8%)	-
≥ 10 units per week (current or past)	5 (7.0%)	-
≥ 20 units per week (current or past)	2 (2.8%)	-

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; FAMMM, familial atypical multiple mole melanoma syndrome; HBOC, hereditary breast and ovarian cancer; MMR, mismatch repair genes; APC, adenomatous polyposis coli; ATM, ataxia telangiectasia mutated; FDR, first degree relative; SDR, second degree relative.

Table 2. Overview of lesion characteristics, type of surgery and pathology in all high-risk individuals who underwent surgery (n=71) and all high-risk individuals who were diagnosed with advanced disease (n=5) while participating in pancreatic cancer surveillance

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)
Lesion characteristics		
Time point of lesion detection:		
Baseline	39 (54.9%)	2 (40.0%)
Follow-up	32 (45.1%)	3 (60.0%)
Present at previous investigations	9 (12.7%)	1 (20.0%)
Mean months of lesion visualization prior to resection/diagnosis (median, range, SD)	8.7 (5.0, 1-32, 9.5)	41 (41, 41, -)
Case overdue for recommended screening	10 (14.1%)	1 (20.0%)
Mean months overdue for recommended screening (median, range, SD)	6.7 (6.0, 1-12, 3.4)	3 (3, 3, -)
Modality that detected the lesion (≥1 option possible):		
EUS	62 (87.3%)	2 (40.0%)
MRI/MRCP	29 (40.8%)	3 (60.0%)
CT / PET-CT	28 (39.4%)	2 (40.0%)
ERCP	8 (11.3%)	-
Lesion type of lesions that were reason for surgery (n=93)		
Cystic	44 (47.3%)	
Solid	33 (35.5%)	
Hypoechoic	3 (3.3%)	
Dilated pancreatic duct	2 (2.2%)	
Features of chronic pancreatitis	1 (1.1%)	
Other	10 (10.8%)	
Lesion location (n=93)		
Head/uncinate region	35 (37.6%)	
Body	20 (21.5%)	
Tail	29 (31.2%)	
No data	9 (9.7%)	
Lesion size in mm, mean (median, range, SD)		

All lesions (n=93)	14.0 (11.9, 3-51, 8.8)	
Cystic lesions (n=44)	13.6 (11.6, 3-40, 8.0)	
Solid lesions (n=33)	15.5 (13.0, 4-51, 10.0)	
Neoadjuvant therapy	4 (5.6%)	N/A
Type of surgery		
Distal pancreatectomy	36 (50.7%)	N/A
Pancreaticoduodenectomy	18 (25.4%)	
Total pancreatectomy	9 (12.7%)	
Pancreaticoduodenectomy followed by completion pancreatectomy	4 (5.6%)	
Central pancreatectomy	2 (2.8%)	
Diagnosis of non-resectable disease during surgery	2 (2.8%)	
Complications of surgery (≥1 option possible)		
None	37 (52.1%)	N/A
Infectious complications	10 (14.1%)	
Delayed gastric emptying	6 (8.5%)	
Pancreatic fistula	4 (5.6%)	
Bile leak	2 (2.8%)	
Peri-pancreatic fluid collection	1 (1.4%)	
Other	6 (8.5%)	
No data	7 (9.9%)	
Pathology (≥1 could be present)		
PDAC	19 (26.8%)	5 (100.0%)
Main-duct IPMN with high-grade dysplasia	1 (1.4%)	-
Main-duct IPMN with moderate-grade dysplasia	4 (5.6%)	-
Main-duct IPMN with low-grade dysplasia	1 (1.4%)	-
Mixed-duct IPMN with high-grade dysplasia	1 (1.4%)	-
Mixed-duct IPMN with moderate-grade dysplasia	-	-
Mixed-duct IPMN with low-grade dysplasia	-	-
Branch-duct IPMN with high-grade dysplasia	5 (7.0%)	-
Branch-duct IPMN with moderate-grade dysplasia	9 (12.7%)	-
Branch-duct IPMN with low-grade dysplasia	16 (22.5%)	-
PanIN-3, multifocal	3 (4.2%)	-
PanIN-3, unifocal	3 (4.2%)	-
PanIN-2, multifocal	35 (49.3%)	-
PanIN-2, unifocal	10 (14.1%)	-
PanIN-1, multifocal	32 (45.1%)	-
PanIN-1, unifocal	4 (5.6%)	-
Pancreatic neuroendocrine tumor ≥ 2 cm	-	-
Pancreatic neuroendocrine tumor < 2 cm	8 (11.3%)	-
Incipient IPMN	5 (7.0%)	-
Serous cystadenoma	2 (2.8%)	-
Vascular malformation	1 (1.4%)	-
Highest grade of neoplastic lesion per HRI		
PDAC	19 (26.8%)	5 (100%)
Stage I/II PDAC	16 (22.5%)	0 (0%)
Stage III/IV PDAC	3 (4.2%)	5 (100%)

Main-duct IPMN with high-grade dysplasia	1 (1.4%)	-
Main-duct IPMN with moderate-grade dysplasia	2 (2.8%)	-
Main-duct IPMN with low-grade dysplasia	1 (1.4%)	-
Branch-duct IPMN with high-grade dysplasia	4 (5.6%)	-
Branch-duct IPMN with moderate-grade dysplasia	7 (9.9%)	-
Branch-duct IPMN with low-grade dysplasia	9 (12.7%)	-
PanIN-3, multifocal	3 (4.2%)	-
PanIN-3, unifocal	2 (2.8%)	-
PanIN-2, multifocal	9 (12.7%)	-
PanIN-2, unifocal	7 (9.9%)	-
PanIN-1, multifocal	1 (1.4%)	-
PanIN-1, unifocal	1 (1.4%)	-
Pancreatic neuroendocrine tumor < 2 cm	3 (4.2%)	-
Serous cystadenoma	2 (2.8%)	-

PDAC, pancreatic ductal adenocarcinoma; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; IPMN, intraductal papillary mucinous neoplasm; PanIN, pancreatic intraepithelial neoplasia; N/A, not applicable.

Table 3. Outcomes in all high-risk individuals who underwent surgery (n=71) and all high-risk individuals who were diagnosed with advanced disease (n=5) while participating in pancreatic cancer surveillance

	High-risk individuals who underwent surgery (n=71) N (%)	High-risk individuals who were diagnosed with advanced PDAC (n=5) N (%)	P-value
Follow-up time in mean months (median, range, SD)	51.6 (42.0, 0-168, 45.1)	8.2 (3.0, 3-28, 11.1)	< 0.001
Survival			
Alive	59 (83.1%)	2 (40.0%)	0.050
Mean months after surgery/diagnosis (median, range, SD)	54.3 (44.0, 0-168, 45.9)	9.5 (3.5, 3-28, 12.3)	< 0.001
Long-term survival (≥ 3 years)	37 (52.1%)	0	
Mortality			
Died	12 (16.9%)	3 (60.0%)	0.050
Mean months after surgery/diagnosis (median, range, SD)	54.3 (28.5, 5-164, 56.0)	11.3 (3.0, 3-28, 14.4)	0.221
Short-term mortality (≤ 1 year)	2 (2.8%)	2 (40.0%)	0.154
PDAC-related	8 (11.3%)	3 (60.0%)	0.506
Non-PDAC-related	2 (2.8%)	0	
Unknown cause of death	2 (2.8%)	0	

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation

Bold P-values were considered statistically significant

Table 4. Univariate and multivariate analyses for factors possibly associated with high-risk neoplastic precursor lesions or pancreatic ductal adenocarcinoma in the resection specimen

Factors	Univariate analyses		Multivariate analyses	
	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age ≥65 at time of surgery	4.108 (1.4-11.7)	0.007	7.530 (1.6-35.0)	0.010
Female gender	3.818 (1.4-10.3)	0.007	5.776 (1.4-24.3)	0.017
White race	0.254 (0.0-2.6)	0.321		
Carrier of a gene mutation	2.395 (0.8-7.2)	0.113	4.918 (1.1-22.6)	0.040
≥2 first-degree relatives affected by PDAC	2.400 (0.9-6.4)	0.076	1.712 (0.4-7.2)	0.462
Family member <50 affected by PDAC	1.150 (0.3-3.8)	0.820		
Body Mass Index ≥25	0.570 (0.2-1.7)	0.303		
Personal history of diabetes	1.829 (0.5-6.8)	0.505		
Personal history of pancreatitis	0.686 (0.2-3.0)	0.727		
Current or former smoker	1.000 (0.4-2.7)	1.000		
>10 pack years of smoking	0.952 (0.1-6.3)	1.000		
Current or former alcohol consumer	0.702 (0.3-1.8)	0.470		
Detection of lesion at follow-up visit	1.142 (0.4-2.9)	0.782		
Solid lesion type (vs cystic lesion)	1.111 (0.4-3.1)	0.839		
Location of lesion in the head/uncinate region (vs location in body/tail)	2.333 (0.8-6.6)	0.105	4.232 (1.1-16.9)	0.041
Lesion size ≥1 centimeter	1.260 (0.4-4.1)	0.702		
Surgery after 2011	1.473 (0.5-4.0)	0.448		

OR, odds ratio; CI, confidence interval; PDAC, pancreatic ductal adenocarcinoma.

Bold P-values were considered statistically significant

Figure 1. Kaplan-Meier survival curve per subgroup

(Figure attached separately)

Legend:

- A. Low-risk neoplastic lesions including pancreatic neuroendocrine tumors (PanNETs) <2 cm (n=39)
- B. High-risk neoplastic lesions including all main-duct intraductal papillary mucinous neoplasms (IPMNs), branch-duct IPMNs with high-grade dysplasia and PanIN-3 lesions (n=13)
- C. Stage I and II PDACs (n=16)
- D. Stage III and IV PDACs (n=8)

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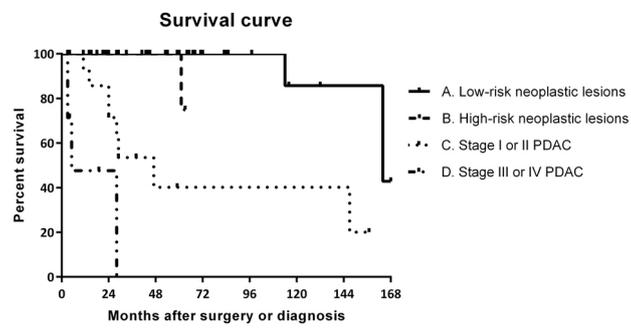
Foot note

No preregistration exists for the reported studies reported in this article

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