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The Netherlands

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# Pancreatic Cancer Surveillance in Carriers of a Germline *CDKN2A* Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up

Derk C.F. Klatte, MD<sup>1</sup>; Bas Boekestijn, MD<sup>2</sup>; Martin N.J.M. Wasser, MD, PhD<sup>2</sup>; Shirin Feshtali Shahbazi, MD<sup>2</sup>; Isaura S. Ibrahim, MD<sup>1</sup>; J. Sven D. Mieog, MD, PhD<sup>3</sup>; Saskia A.C. Luelmo, MD<sup>4</sup>; Hans Morreau, MD, PhD<sup>5</sup>; Thomas P. Potjer, MD, PhD<sup>6</sup>; Akin Inderson, MD<sup>1</sup>; Jurjen J. Boonstra, MD, PhD<sup>1</sup>; Friedo W. Dekker, PhD<sup>7</sup>; Hans F.A. Vasen, MD, PhD<sup>1</sup>; Jeanin E. van Hooft, MD, PhD, MBA<sup>1</sup>; Bert A. Bonsing, MD, PhD<sup>2</sup>; and Monique E. van Leerdam, MD, PhD<sup>1,8</sup>

**PURPOSE** Pancreatic cancer surveillance in high-risk individuals may lead to detection of pancreatic ductal adenocarcinoma (PDAC) at an earlier stage and with improved survival. This study evaluated the yield and outcomes of 20 years of prospective surveillance in a large cohort of individuals with germline pathogenic variants (PVs) in *CDKN2A*.

**METHODS** Prospectively collected data were analyzed from individuals participating in pancreatic cancer surveillance. Surveillance consisted of annual magnetic resonance imaging with magnetic resonance cholangiopancreatography and optional endoscopic ultrasound.

**RESULTS** Three hundred forty-seven germline PV carriers participated in surveillance and were followed for a median of 5.6 (interquartile range 2.3-9.9) years. A total of 36 cases of PDAC were diagnosed in 31 (8.9%) patients at a median age of 60.4 (interquartile range 51.3-64.1) years. The cumulative incidence of primary PDAC was 20.7% by age 70 years. Five carriers (5 of 31; 16.1%) were diagnosed with a second primary PDAC. Thirty (83.3%) of 36 PDACs were considered resectable at the time of imaging. Twelve cases (12 of 36; 33.3%) presented with stage I disease. The median survival after diagnosis of primary PDAC was 26.8 months, and the 5-year survival rate was 32.4% (95% CI, 19.1 to 54.8). Individuals with primary PDAC who underwent resection (22 of 31; 71.0%) had an overall 5-year survival rate of 44.1% (95% CI, 27.2 to 71.3). Nine (2.6%; 9 of 347) individuals underwent surgery for a suspected malignant lesion, which proved to not be PDAC, and this included five lesions with low-grade dysplasia.

**CONCLUSION** This long-term surveillance study demonstrates a high incidence of PDAC in carriers of a PV in *CDKN2A*. This provides evidence that surveillance in such a high-risk population leads to detection of early-stage PDAC with improved resectability and survival.

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## ASSOCIATED CONTENT

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## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease, which is expected to become the leading cause of cancer-related mortality by 2030.<sup>1</sup> There is a tremendous need for earlier detection, as it is evident that resected stage I tumors have by far the most favorable prognosis.<sup>2</sup>

Population-based screening for average-risk individuals is not recommended. The overall incidence of PDAC is too low and will therefore result in large numbers of false positives.<sup>3</sup>

For high-risk individuals (HRIs), however, who are with a strong family history or carriers of specific germline pathogenic variants (PVs),<sup>4-6</sup> evidence has accumulated

that surveillance leads to detection of PDAC at an earlier stage, higher resectability, and improved survival.<sup>7,8</sup> However, although a recent cohort study found a substantial diagnostic yield of PDAC in carriers of high-risk PVs,<sup>9</sup> surveillance did not evidently translate into improved outcomes, so effectiveness of pancreatic cancer surveillance is still under debate.

Over the past 2 decades, multiple expert centers have developed imaging-based pancreatic cancer surveillance programs.<sup>8,10-12</sup> One such surveillance program for *CDKN2A* PV carriers was initiated in 2000 at the Leiden University Medical Center (LUMC). The majority of this population carries a specific Dutch founder PV in *CDKN2A* known as *p16-Leiden* (c.225\_243del19). *CDKN2A/p16-Leiden* PV carriers are at an estimated

## CONTEXT

### Key Objective

Individuals at high risk of pancreatic ductal adenocarcinoma (PDAC) may benefit from participation in surveillance programs. This long-term follow-up study of a unique, large cohort of individuals with a germline *CDKN2A* pathogenic variant (PV) aimed to assess the benefit of pancreatic cancer surveillance in this population.

### Knowledge Generated

Carriers of a germline PV in *CDKN2A* are at a high lifetime risk of PDAC. Surveillance in this population leads to diagnosis of stage I disease in one third of patients, which resulted in increased resectability and a substantial 5-year survival rate of 32.4%.

### Relevance

Previous evaluations of surveillance programs for high-risk individuals have demonstrated varying results. Taking the outcomes of this study into account, a benefit of surveillance seems to be particularly attainable in individuals with a proven PV, who are at highest risk of developing PDAC.

70% lifetime risk of melanoma and a 15%-20% lifetime risk of pancreatic cancer.<sup>13</sup> Evaluations of surveillance in this high-risk cohort have been previously published in 2011 and 2016.<sup>7,14</sup> Key findings were increased resectability (75%) and survival (5-year survival rate of 24%) compared with PDAC in the general population, which were based on an analysis of 178 carriers of a *CDKN2A* PV.<sup>7</sup> Although these results are promising, it is important to evaluate if surveillance increases diagnosis of stage I PDAC, which is currently viewed as the goal of a beneficial pancreatic cancer surveillance program.<sup>4</sup>

In this study, we present an update of our pancreatic cancer surveillance program, in which we report on the yield and outcomes of a 20-year prospective follow-up of a unique and large cohort of germline *CDKN2A* PV carriers. In addition, we assess whether surveillance in this population leads to detection of early-stage PDAC with higher resection rates and improved prognosis.

## METHODS

### Study Design and Population

This study is an analysis of prospectively collected data from an ongoing surveillance program initiated in 2000 at LUMC for carriers of a germline *CDKN2A* PV. Individuals with a proven pathogenic or likely pathogenic germline *CDKN2A* variant were referred from the Department of Clinical Genetics to the Department of Gastroenterology and Hepatology. All participants provided written informed consent before enrollment in the surveillance program. This study was approved by the institutional review board of the LUMC (MEC P00.107; P21.006) and was registered at the Netherlands Trial Register (NL9158). Enrollment in the surveillance program was selected as the start of follow-up. Surveillance data were evaluated up to November 1, 2021.

### Surveillance Protocol

A detailed description of the surveillance protocol is provided in [Appendix 1](#) (online only). In summary, surveillance was initially offered at age 45 years, or 10 years before the youngest age of familial onset.<sup>15</sup> In 2020, following the International Cancer of the Pancreas Screening Consortium guideline,<sup>4</sup> the age of enrollment was lowered to 40 years. Surveillance consisted of a dedicated magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography protocol every  $12 \pm 1$  months. Since 2012, participants were able to also receive an optional endoscopic ultrasound (EUS) every 12 months, alternating every 6 months with MRI. Thus, individuals participating in both MRI and EUS surveillance underwent screening every 6 months. Cases were discussed in a multidisciplinary team consisting of surgeons, radiologists, oncologists, pathologists, and gastroenterologists, in which a decision was made on the necessity for surgical resection.<sup>16-19</sup>

### Definitions and Data Collection

Data on demographics, lifestyle, and family and medical history were collected at baseline and during follow-up. All imaging findings and EUS-guided cytologic samples were reported in the database. In the case of multiple pancreatic lesions, the highest pathologic grade was used for study end points. Malignant lesions were coded according to the Union for International Cancer Control TNM classification, eighth edition. The date of diagnosis was based on the date of cytologic or histopathologic diagnosis or the date on which a suspicious lesion was diagnosed on imaging when no pathologic sample was obtained. The pathologic stage was selected over the clinical stage when histopathologic examination was available. For patients who received neoadjuvant chemotherapy, both the clinical stage and the pathologic stage are presented. Detected lesions were defined as prevalent when present at first screening and incident

when diagnosed during surveillance. Analogous to the World Endoscopy Organization definition of interval carcinomas in colorectal cancer screening,<sup>20</sup> an interval cancer was defined as a diagnosis after a screening examination in which no cancer was detected, before the next recommended examination within 12 months.

### Outcomes

Outcomes to report on the yield of surveillance were the number and nature of pancreatic abnormalities, characteristics of patients developing PDAC, the cumulative incidence of PDAC during follow-up, PDAC stage, surgical resection rate, and survival rates.

### Statistical Analysis

Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR), depending on the distribution, and categorical variables as frequencies and percentage of total. For primary PDAC, incidence rates per 1,000 person-years of follow-up were calculated with their corresponding 95% CI on the basis of normal distribution. Kaplan-Meier survival analysis was used to estimate the cumulative incidence and survival of primary PDAC. All analyses were performed using R version 4.0.2.

## RESULTS

Three hundred forty-seven *CDKN2A* PV carriers participated in the LUMC pancreatic cancer surveillance program, of whom 342 (98.6%) carry the *p16-Leiden* PV (Table 1). For this study, 169 participants have been included since the previous analysis in 2016.<sup>7</sup> One hundred forty-six (42.1%) were male, and the median age of enrollment in the surveillance program was 48.6 (IQR 44.5-55.7) years. Of the total study population, 133 (38.3%) had at least one first-degree relative and 119 (34.6%) had at least 1 second-degree relative with PDAC. Individuals were followed for a total of 2,189 person-years with a median of 5.6 (IQR 2.3-9.9) years. Ninety-six (19.8%) individuals participated in both MRI and EUS surveillance. In total, 2,098 MRI (median 5; IQR 2-7) and 208 EUS (median 2; IQR 1-4; n = 69) for surveillance were performed until the end of data collection (November 1, 2021).

### Summary of Pancreatic Ductal Adenocarcinoma Cases

A total of 36 cases of PDAC were detected in 31 (31 of 347; 8.9%) patients (Tables 2-4). Primary PDAC was diagnosed at a median age of 60.4 (51.3-64.1) years. Five (16.1%) of 31 patients were diagnosed with a second PDAC (Table 4), which are described in detail in Appendix 2 (online only).<sup>21,22</sup> Individuals were followed for a median of 5.7 (IQR 0.6-10.0) years until diagnosis of primary PDAC. The incidence rate of primary PDAC was 14.2 (95% CI, 9.6 to 20.1) cases per 1,000 person-years at risk, corresponding to an estimated cumulative incidence of 7.3% by age 60 years and 20.7% by age 70 years (Fig 1). Of all cases, approximately one fifth (8 of 36; 22.9%) were diagnosed at

first screening (prevalent PDAC) and the majority (29 of 36; 80.6%) of PDAC were detected with MRI. Five (5 of 36; 13.8%) PDACs were detected with computed tomography, and one (1 of 36; 2.7%) with abdominal ultrasound in patients who presented with symptoms or as an incidental finding outside of planned follow-up visit. In four (4 of 36; 11.1%) cases, surveillance was delayed and PDAC was diagnosed after the recommended interval of 12 + 1 months (15-28 months). In four cases (4 of 36; 11.1%) with no histologic confirmation, diagnosis was based on imaging findings. In the past 5 years, six (50.0%) of 12 cases detected through screening had stage I cancer, and six had a T1 tumor (Tables 3 and 4; Appendix Fig A1, online only). Notably, in the same period, 20.0% (3 of 15) of patients presented with interval cancers, as compared with 9.5% (2 of 21) in the preceding 15 years.

### Management of PDAC Cases (n = 36)

Thirty (83.3%) of 36 PDAC cases in 31 patients were considered to have resectable disease at the time of imaging (Table 2). A flowchart of the management of these patients is depicted in Appendix Figure A2 (online only). Three (3 of 36; 8.3%) patients with resectable disease did not have surgery. One patient (P3) had a concomitant metastatic melanoma. The second patient (P16) refused to undergo surgery. The third patient (P31) chose an alternative treatment with transarterial chemoembolization and microwave ablation elsewhere. In total, 27 (75.0%) of the 36 PDACs were resected. Four (4 of 36; 11.1%) cases (P27-P29, P17) were treated with neoadjuvant chemotherapy in the trial setting before surgical resection. Stage I PDAC was detected in 12 (33.3%) of 36 cases.

### Survival Outcomes in Individuals After Diagnosis of Primary PDAC (n = 31)

In total, 18 (58.1%) of 31 patients died of PDAC. One (3.2%) patient died of melanoma metastasis, and one (3.2%) patient with metastasized PDAC died of trauma. The median overall survival time after diagnosis of primary PDAC was 26.8 months (IQR 20.6 to not available), and the overall 5-year survival rate was 32.4% (95% CI, 19.1 to 54.8; Fig 2A). Individuals who underwent pancreatic resection for primary PDAC (22 of 31; 71.0%) had an overall 5-year survival rate of 44.1% (95% CI, 27.2 to 71.3). Six (19.4%) individuals who were diagnosed with primary PDAC stage I and who underwent surgical resection reached an overall 3-year survival of 83.3%. Patients diagnosed with primary PDAC in 2011-2021 (23 of 31; 74.1%) had a trend for a more favorable prognosis than those diagnosed in 2000-2010 (8 of 31; 25.8%); the overall 3-year survival was 39.7% versus 12.5%, respectively (log-rank  $P = .095$ ; Fig 2B). Survival did not differ between individuals with primary PDAC localized in the head (n = 14; 45.1%) versus body or tail (n = 17; 54.8%; log-rank  $P = .80$ ; Appendix Fig A3, online only). There was no perioperative mortality after pancreatic resection.

**TABLE 1.** Characteristics of *CDKN2A* Pathogenic Variant Carriers (N = 347) Who Underwent Pancreatic Cancer Surveillance

Characteristic	Total Population (N = 347)
Age at start of surveillance, years	48.6 (44.5-55.7)
Male	146 (42.1)
BMI	25.6 (23.2-28.3)
<i>CDKN2A</i> mutation	
p16-Leiden	342 (98.6)
Others <sup>a</sup>	5 (1.4)
First-degree relative with PDAC	
1	108 (31.1)
2	22 (6.3)
3 or more	3 (0.9)
Second-degree relative with PDAC	
1	80 (23.1)
2	29 (8.4)
3 or more	11 (3.2)
Smoking	
Never	156 (45.0)
Former	151 (43.5)
Current	33 (9.5)
Unknown	7 (2.0)
Alcohol consumption	
Abstinent	73 (21.2)
< 7 units/wk	137 (39.0)
7-20 units/wk	85 (24.4)
> 20 units/wk	22 (6.4)
Past or unknown	30 (8.6)
Personal history of malignancies	
Melanoma	191 (55.0)
Oropharyngeal or laryngeal	18 (5.2)
Upper GI	5 (1.4)
Others <sup>b</sup>	40 (11.5)

NOTE. Data are median (interquartile range) or No. (%).

Abbreviations: BMI, body mass index; PDAC, pancreatic ductal adenocarcinoma.

<sup>a</sup>c.67G>C, p.(Gly23Arg); c.143C>G, p.(Pro48Arg); c.143C>A, p.(Pro48Gln); c.47T>G, p.(Leu16Arg); c.176T>G, p.(Val59Gly).

<sup>b</sup>All other malignancies, excluding basal cell carcinoma.

### Surgery for Other Pancreatic Lesions Detected by Surveillance

Nine (2.6%) of 347 individuals underwent surgery for a lesion suspected of malignancy and were found to not have PDAC (Appendix Table A1, online only). One patient had an early-stage (pT1aNOM0) ampullary carcinoma; one had a grade 1 neuroendocrine tumor (pT1NOM0); five (5 of 36; 14%) had precursor lesions with low-grade dysplasia, of whom one had a concurrent

GI stromal tumor in the stomach, which was resected; one had signs of ductal proliferation with chronic inflammation, and one diffuse islet cell hyperplasia. All these patients were alive at the time of analysis after a median follow-up time of 29 (IQR 25-35) months. The diagnostic workup before surgery of these cases is described in more detail in [Appendices 1-3](#).

### DISCUSSION

In this 20-year prospective follow-up study of a unique, large cohort of *CDKN2A* PV carriers, we demonstrate that pancreatic cancer surveillance leads to detection of resectable, early-stage PDAC with a favorable prognosis. This study encompasses the largest number of PDAC cases detected in pancreatic cancer surveillance to date, in which we present outcomes that are notably better than what is currently reported for individuals diagnosed with PDAC in the general population.<sup>23</sup> These data add to the accumulating evidence that surveillance for certain HRIs may be beneficial.

Approximately one fifth of this population was found to develop PDAC by age 70 years. This cumulative risk is the highest currently reported for *CDKN2A* in the literature and is among the highest of all known PDAC susceptibility genes.<sup>24,25</sup> More than 80% of patients were found to have resectable disease, and one third was diagnosed with stage I PDAC. Compared with sporadic PDAC with only 10%-15% of resectable cases, these results are very promising. This is also reflected in the relatively high 5-year overall survival rate of 32.4% in this high-risk population under surveillance compared with only 5% of PDAC diagnosed in the general population.<sup>1</sup> Survival appeared to be more favorable for patients diagnosed in the past decade, as compared with 2000-2010. This could be explained by improved imaging, leading to earlier diagnosis of PDAC, centralization of PDAC care in the Netherlands,<sup>26</sup> and improved therapy, including the introduction of neo-adjuvant chemotherapy.<sup>27</sup> It is worth noting that in the same period, a relatively large proportion of cases presented as interval cancers. Recently, we have retrospectively assessed MRI examinations of incident and interval cases.<sup>28</sup> We observed that in 75%, direct or indirect signs of a tumor were present on previous examinations. Awareness of these (often subtle) findings offers an opportunity for expert radiologists to detect these lesions at an earlier stage and will potentially result in a decrease of interval tumors.

Over the past 2 decades, several centers have reported on the yield and outcomes of their surveillance programs conducted in various high-risk populations with varying outcomes. Canto et al<sup>8</sup> conducted a large prospective multicenter study in the United States, including 354 HRI with a 16-year follow-up and found that nine of 10 PDACs were resectable with a high 3-year survival rate of 85%. In this study, 10 patients did undergo resection of a lesion with high-grade dysplasia who reached a 5-year survival rate of

**TABLE 2.** Summary of PDAC Cases (n = 36) Diagnosed in 31 Patients While Participating in Pancreatic Cancer Surveillance

Characteristic	PDAC Cases (n = 36)
Primary PDAC <sup>a</sup>	31 (8.9)
Second PDAC <sup>b</sup>	5 (16.1)
Synchronous	1 (3.2)
Metachronous	4 (12.9)
Age at diagnosis of primary PDAC, years	60.4 (51.3-64.1)
Male <sup>c</sup>	11 (35.5)
Year of diagnosis of primary PDAC	
2000-2005	3 (9.7)
2006-2010	5 (16.1)
2011-2015	6 (19.4)
2016-2021	17 (54.8)
Diagnosed at first screening (prevalent)	8 (22.2)
Diagnosed during follow-up (incident)	28 (77.8)
Interval cancer	6 (17.1)
Detection modality	
MRI/MRCP	29 (80.6)
EUS	1 (2.8)
CT	5 (13.9)
Abdominal ultrasound	1 (2.8)
Localization	
Head	16 (44.4)
Body/tail	20 (55.6)
Resectable	30 (83.3)
Underwent surgery	27 (75.0)
Tumor-free resection margins (R0)	20 (74.1)
Stage	
IA	9 (25.0)
IB	3 (8.3)
IIA	7 (19.4)
IIB	4 (11.1)
III	9 (25.0)
IV	4 (11.1)

NOTE. Data are median (interquartile range) or No. (%).

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; MRI/MRCP, magnetic resonance imaging with magnetic resonance cholangio-pancreatography; PDAC, pancreatic ductal adenocarcinoma.

<sup>a</sup>Proportion of primary PDAC cases was calculated from the total study population (N = 347).

<sup>b</sup>Proportions of second PDAC cases were calculated from the total number of primary PDAC cases (n = 31).

<sup>c</sup>Proportion of male was calculated from the total study population (N = 347).

100%. In our current study, we were not able to detect any cases with only high-grade dysplasia. Detection of high-grade dysplasia has thus far proven to be extremely challenging, mainly because of the lack of specific imaging

findings for pancreatic intraepithelial neoplasia. It is important to consider, however, that half (24 of 48) of all resected HRI in the US cohort had low-grade precursor lesions on histopathologic evaluation, representing 7% of the total cohort.<sup>29</sup> This highlights an important trade-off between aggressiveness of treatment decisions and risk of false-positive findings, with a substantial risk of mortality and long-term morbidity.<sup>30</sup> In our program, seven (2.0%) individuals underwent surgery for a suspicion of malignancy and appeared to have benign pathology. A Dutch multicenter, prospective study recently reported on their long-term surveillance outcomes and compared the yield between HRIs with (n = 265) and without (n = 165) a known PDAC susceptibility gene variant (familial pancreatic cancer kindreds).<sup>9</sup> Of note, all 10 PDAC cases were diagnosed in germline PV carriers—of which, 7 *CDKN2A* PV carriers—and no PDAC was diagnosed in the PV-negative HRIs. Importantly, more than half of the unnecessary resections (n = 11) were performed in the PV-negative group. These observations support to preserve pancreatic cancer surveillance for individuals who are at highest risk to maximize potential benefits while minimizing harms of overtreatment. Our results are not yet generalizable to groups with a lower PDAC risk. Future efforts should focus on discovery of reliable biomarkers, which ideally distinguishes low-grade and high-grade precursor lesions, avoiding unnecessary interventions, while intervening at the earliest stage possible.

A major concern in evaluating effectiveness of screening is that any observed survival benefit is largely attributable to lead-time bias. Although the exact influence of this bias is difficult to ascertain, we are confident that not all the observed benefit in this study is attributable to lead time. More than 80 percent had a resectable tumor, and after resection of primary PDAC, approximately half reached 5-year survival. Particularly, in the past 5 years, a relatively large number of stage I cancers were detected, which may be a consequence of enhancements of a dedicated MRI protocol.<sup>28</sup> When resected, the 3-year survival of these cancers (n = 6) reached more than 80%, which is even higher than resected stage I PDAC in the general population (50%).<sup>2</sup> Since effects of lead time are most prominent in short-term survival, future studies assessing long-term (10-year) survival will likely give a more reliable appraisal of a true survival benefit.

An important finding is that *CDKN2A* PV carriers are at a substantial risk of multiple PDACs. Five (16.1%) of 31 patients were diagnosed with a second PDAC, of which four were metachronous cancers occurring up to 9 years after primary PDAC. Although a considerable proportion of PDAC survivors in the general population appears at risk of second PDAC (6%), the ratio in our population appears more than twice as high.<sup>31</sup> We expect this number to further increase as a larger number of patients with early-stage cancer will reach long-term

**TABLE 3.** Details of Patients Who Were Diagnosed With Primary PDAC (n = 31) During Surveillance

No.	Diagnosis Year	Age at Diagnosis, years/Sex	Follow-Up Duration, months	Prior Screening Modality	Time Since Previous Screening, months	Detection Modality	Interval Cancer	Management	Cytologic or Histopathologic Results	TNM Stage	Outcome/Survival Time From Diagnosis, months	Cause of Death
P1 <sup>a</sup>	2002	57/F	4	MRI/MRCP	4	CT	Yes	No surgery	Poorly differentiated adenocarcinoma of pancreatobiliary origin	cT4NxM1	Died/15	PDAC
P2	2003	72/F	21	MRI/MRCP	11	MRI/MRCP	No	DP	Moderately differentiated PDAC, R1 resection	pT4N1M0	Died/3	PDAC
P3 <sup>b</sup>	2004	58/M	35	MRI/MRCP	5	MRI/MRCP	No	No surgery	Not obtained	cT1bNOM0	Died/10	Melanoma metastasis
P4	2006	57/M	39	MRI/MRCP	12	MRI/MRCP	No	DP	Moderately differentiated PDAC, R2 resection	pT4N2M0	Died/21	PDAC
P5	2008	57/F	34	MRI/MRCP	28	MRI/MRCP	No	DP	Moderately differentiated PDAC, R0 resection	pT2NOM0	Died/21	PDAC
P6	2008	62/F	3	—	—	MRI/MRCP	No	PPPD	Well-differentiated PDAC, R0 resection	pT3NOM0	Alive/153	—
P7	2009	48/M	3	—	—	MRI/MRCP	No	DP	Poorly differentiated PDAC, R0 resection	pT3NOM0	Died/34	PDAC
P8	2010	47/F	4	—	—	MRI/MRCP	No	DP	Poorly differentiated PDAC, R0 resection	pT3N2M0	Died/17	PDAC
P9	2011	63/F	91	MRI/MRCP	11	MRI/MRCP	No	No surgery	Adenocarcinoma of pancreatobiliary origin	cT2N2M0	Died/8	PDAC
P10	2012	39/M	17	—	—	MRI/MRCP	No	PPPD	Moderately differentiated PDAC, R0 resection	pT2N2M0	Alive/115	—
P11	2012	55/F	131	MRI/MRCP	12	MRI/MRCP	No	DP	Moderately differentiated PDAC, R0 resection	pT3NOM0	Died/31	PDAC
P12	2014	66/F	143	MRI/MRCP	22	CT	No	No surgery	Adenocarcinoma of pancreatobiliary origin	cT4NOM0	Died/9	PDAC
P13	2014	58/M	91	MRI/MRCP	10	CT	Yes	No surgery	Not obtained	cT4NOM0	Died/27	PDAC
P14	2014	74/F	83	MRI/MRCP	12	MRI/MRCP	No	DP	Moderately differentiated PDAC, R0 resection	pT1cNOM0	Alive/87	—
P15	2015	50/M	44	MRI/MRCP	9	MRI/MRCP	No	PPPD	Moderately differentiated PDAC, R1 resection	pT3NOM0	Died/20	PDAC
P16 <sup>c</sup>	2016	64/F	2	—	—	MRI/MRCP	No	No surgery	Not obtained	cT2NOM0	Died/16	PDAC
P17	2016	51/F	86	MRI/MRCP	5	Abdominal ultrasound	Yes	DP	Well-differentiated PDAC, R0 resection	pT3NOM0	Alive/63	—
P18	2016	67/F	119	MRI/MRCP	11	MRI/MRCP	No	PPPD	Moderately differentiated PDAC, R0 resection	pT3N1M0	Died/22	PDAC
P19	2016	62/M	68	MRI/MRCP	12	MRI/MRCP	No	PPPD	Poorly differentiated periampullary PDAC, R0 resection	pT1cN1M0	Died/21	PDAC
P20	2016	61/F	161	MRI/MRCP	12	MRI/MRCP	No	TP	Poorly differentiated PDAC, R0 resection	pT1aNOM0	Alive/57	—
P21	2017	65/M	172	MRI/MRCP	8	CT	Yes	PPPD	Moderately differentiated PDAC, R0 resection	pT3NOM0	Alive/51	—

(continued on following page)

**TABLE 3.** Details of Patients Who Were Diagnosed With Primary PDAC (n = 31) During Surveillance (continued)

No.	Diagnosis Year	Age at Diagnosis, years/Sex	Follow-Up Duration, months	Prior Screening Modality	Time Since Previous Screening, months	Detection Modality	Interval Cancer	Management	Cytologic or Histopathologic Results	TNM Stage	Outcome/Survival Time From Diagnosis, months	Cause of Death
P22	2017	63/M	7	MRI/MRCP	3	MRI/MRCP	No	PPPD	Moderately differentiated PDAC originated from IPMN, R0 resection	pT1bN0M0	Alive/47	—
P23	2017	71/M	71	MRI/MRCP	13	MRI/MRCP	No	PPPD	Well-differentiated PDAC, R0 resection	pT3N0M0	Died/36	Other causes
P24	2018	49/F	3	—	—	MRI/MRCP	No	Neoadjuvant chemotherapy, surgery discontinued	Adenocarcinoma of pancreatobiliary origin	cT4N0M1	Died/15	PDAC
P25	2018	69/F	211	MRI/MRCP	13	MRI/MRCP	No	DP	Moderately differentiated PDAC, R0 resection	pT2N2M0	Alive/38	—
P26	2018	63/F	127	MRI/MRCP	12	MRI/MRCP	No	PPPD	Moderately differentiated PDAC, R1 resection	pT2N0M0	Alive/40	—
P27	2018	59/F	7	—	—	MRI/MRCP	No	Neoadjuvant chemotherapy + DP	PDAC, partial regression (> 5% residual tumor), R2 resection	cT4N0M0, ypT4N2M0	Died/21	PDAC
P28	2019	48/F	121	MRI/MRCP	16	MRI/MRCP	No	Neoadjuvant chemotherapy + PPPD	PDAC, partial regression (> 5% residual tumor), R1 resection	cT2N0M0, ypT2N1M0	Alive/31	—
P29	2019	60/F	3	—	—	MRI/MRCP	No	Neoadjuvant chemotherapy + PPPD	PDAC, almost complete regression (< 5% residual tumor), R0 resection	cT1cN0M0, ypT1aN0M0	Alive/23	—
P30	2020	61/M	125	MRI/MRCP	4	CT	Yes	No surgery	Adenocarcinoma with a strong suspicion of pancreatobiliary origin	cT4N1M1	Died/1	PDAC
P31 <sup>d</sup>	2020	50/F	88	MRI/MRCP	8	MRI/MRCP	No	Transarterial chemoembolization and microwave ablation, awaiting surgery	Fine-needle biopsy: at least high-grade dysplasia	cT1bN0M0	Alive/12	—

NOTE. Patient numbers (No.) in italics were reported in previous publications.

Abbreviations: CT, computed tomography; DP, distal pancreatectomy; F, female; IPMN, intraductal papillary mucinous neoplasm; M, male; MRI/MRCP, magnetic resonance imaging with magnetic resonance cholangiopancreatography; PDAC, pancreatic ductal adenocarcinoma; PPPD, pylorus-preserving pancreaticoduodenectomy; R, resectable; TP, total pancreatectomy.

<sup>a</sup>This interval PDAC was missed on first MRI examination.

<sup>b</sup>This patient had a concomitant melanoma metastasis and did therefore not have surgery. On the basis of revision of MRI, the differential diagnosis of the pancreatic lesion is a melanoma metastasis. Histologic confirmation was not obtained.

<sup>c</sup>Patient refused to undergo surgery.

<sup>d</sup>Patient's decision to undergo an alternative treatment with transarterial chemoembolization and microwave ablation, which was not advised by our multidisciplinary team.

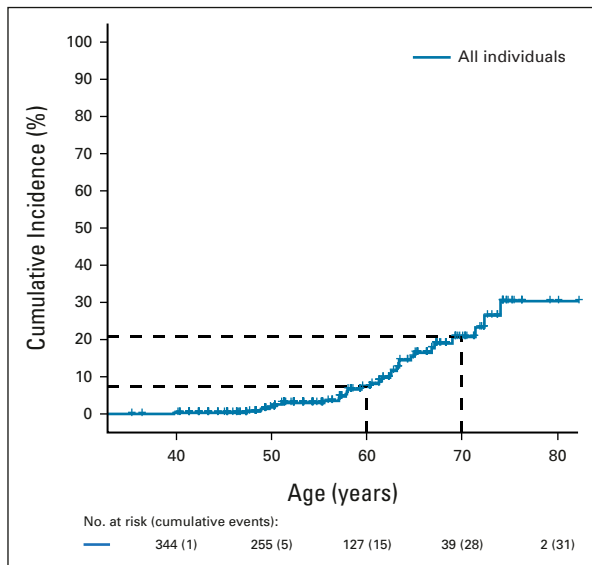


**TABLE 4.** Details of Patients Who Were Diagnosed With Second PDAC (n = 5) During Surveillance

No.	Diagnosis Year	Age at Diagnosis, years/Sex	Follow-Up Duration, months	Prior Screening Modality	Time Since Previous Screening, months	Detection Modality	Interval Cancer	Management	Cytologic or Histopathologic Results	Synchronous or Metachronous	TNM Stage	Outcome/Survival Time From Diagnosis, months	Cause of Death
P6	2013	67/F	59	EUS	1	EUS	No	DP	One duct with suspected malignancy and PanIN with high-grade dysplasia, R0 resection	Metachronous	pT1aN0M0	Alive/95	—
P18 <sup>a</sup>	2017	67/F	126	MRI/MRCP	6	MRI/MRCP	Yes	TP	Moderate-poorly differentiated PDAC, R0 resection	Synchronous	pT3N0M1	Died/15	PDAC
P22	2020	66/M	41	MRI/MRCP	11	MRI/MRCP	No	DP	Moderately differentiated PDAC, R0 resection	Metachronous	pT1bN0M0	Alive/10	—
P17	2021	55/F	142	MRI/MRCP	7	MRI/MRCP	No	Neoadjuvant chemotherapy + PD	PDAC, partial regression (> 5% residual tumor), R0 resection	Metachronous	cT2N0M0, ypT1cN0M0	Alive/4	—
P10	2021	49/M	131	MRI/MRCP	15	MRI/MRCP	No	DP + adjuvant chemotherapy planned	Moderately differentiated PDAC, R1 resection	Metachronous	pT1cN1M0	Alive/1	—

Abbreviations: DP, distal pancreatectomy; EUS, endoscopic ultrasound; F, female; M, male; MRI/MRCP, magnetic resonance imaging with magnetic resonance cholangiopancreatography; PanIN, pancreatic intraepithelial neoplasia; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; R, resectable; TP, total pancreatectomy.

<sup>a</sup>This synchronous PDAC was detected by retrospective assessment of the preoperative MRI before surgical resection of the primary PDAC and subsequently underwent a total pancreatectomy.



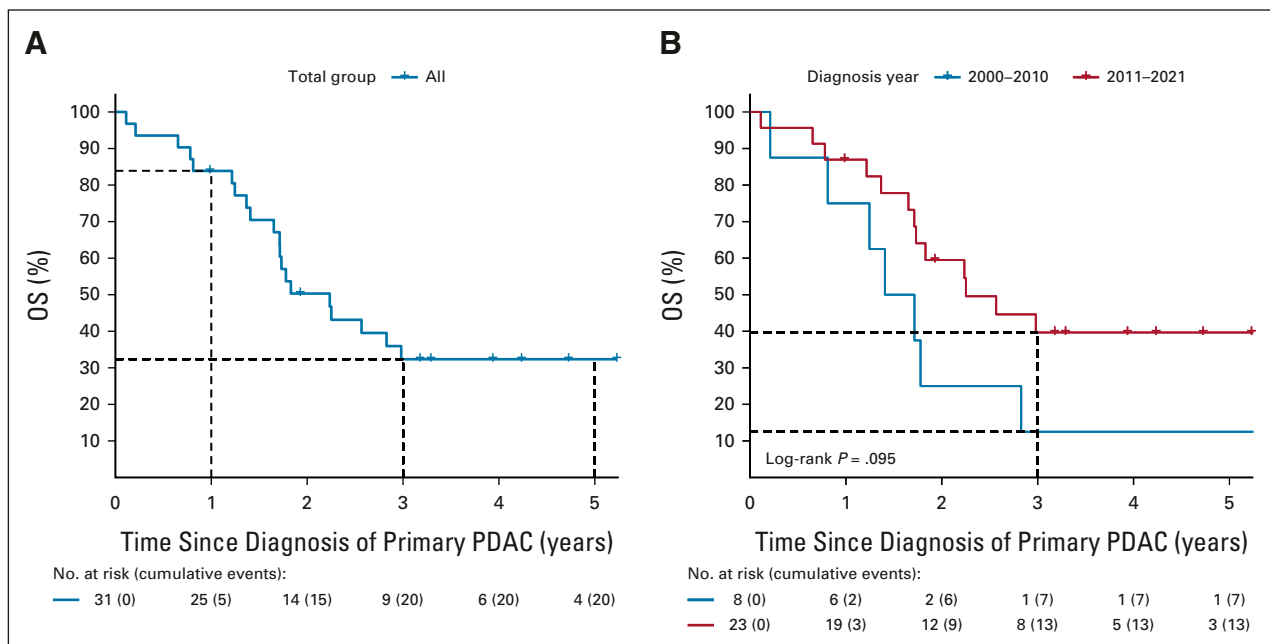
**FIG 1.** Cumulative incidence of primary pancreatic ductal adenocarcinoma (n = 31) in *CDKN2A* pathogenic variant carriers (N = 347) participating in surveillance.

survival. A likely pathophysiologic basis is that loss of heterozygosity of *CDKN2A* occurs in multiple regions, causing multiple malignant precursors to originate in the pancreas. One case report of a *CDKN2A* PV carrier with a second PDAC 7 years after primary PDAC showed distinct mutation profiles between the two lesions, which made a local recurrence unlikely.<sup>22</sup> The increased risk of second PDAC has important clinical consequences.

In the first place, we advocate that after a partial pancreatectomy with a diagnosis of PDAC or a high-grade precursor lesion, intensified surveillance with imaging every 6 months may be beneficial. Furthermore, in patients with small, early-stage PDAC without evidence of lymph node metastasis, a total pancreatectomy may be considered. We acknowledge that a major drawback in offering a total pancreatectomy is the development of diabetes with substantial long-term morbidity.<sup>32</sup> Intraportal islet auto-transplantation may offer a future solution to substantially decrease risk of pancreatogenic diabetes.<sup>33</sup> Further research is necessary to evaluate feasibility of total pancreatectomy.

A major strength of this study is the prospective, long-term follow-up of a highly selected population of proven *CDKN2A* PV carriers. These results are valuable for the management of *CDKN2A* PV carriers in other centers and add to the scarce data on outcomes of pancreatic cancer surveillance. Another strength is that surveillance was performed in a highly dedicated and experienced multidisciplinary team.<sup>28</sup>

This study has several limitations. First, although this study records one of the longest follow-up time thus far, the majority of cases were diagnosed in the past decade. The lack of long-term follow-up data limits conclusions on a long-term survival benefit. Second, the homogeneity of this population limits generalizability to other high-risk surveillance programs. Finally, a relatively small proportion of individuals underwent EUS surveillance, and as a consequence, a low number of EUS (n = 208) as compared with MRI (n = 2,098) were performed, which



**FIG 2.** Kaplan-Meier curves for OS of *CDKN2A* pathogenic variant carriers after diagnosis of primary PDAC (n = 31): (A) OS of primary PDAC cases in total and (B) OS stratified by year of diagnosis: 2000-2010 in blue (n = 8) and 2011-2021 in red (n = 23). The maximum follow-up duration was 12.5 years. OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

hinders comparison of the diagnostic accuracy of these two imaging modalities.

In conclusion, in this 20-year prospective follow-up study, we demonstrate that individuals with a germline *CDKN2A*

PV are at high risk of primary and second PDACs. Our outcomes support the evidence that pancreatic cancer surveillance in individuals at high risk leads to detection of early-stage, resectable PDAC with improved survival.

## AFFILIATIONS

<sup>1</sup>Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

<sup>2</sup>Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

<sup>3</sup>Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands

<sup>4</sup>Department of Oncology, Leiden University Medical Center, Leiden, the Netherlands

<sup>5</sup>Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands

<sup>6</sup>Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands

<sup>7</sup>Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

<sup>8</sup>Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands

## CORRESPONDING AUTHOR

Derk C.F. Klatte, MD, Department of Gastroenterology and Hepatology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands; Twitter: @Derkklatte1; e-mail: d.c.f.klatte@lumc.nl

## PRIOR PRESENTATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## DATA SHARING STATEMENT

Upon publication of the manuscript, patient data, including demographics, personal and family cancer history, and follow-up data, and the study protocol will be available upon written request. Please send inquiries to the corresponding author including a detailed proposal of how data will be handled. A data use agreement must be constructed before any data will be transferred.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Derk C.F. Klatte, Hans F.A. Vasen, Jeanin E. van Hooft, Monique E. van Leerdam

**Provision of study materials or patients:** Derk C.F. Klatte, Bas Boekestijn, Martin N.J.M. Wasser, Shirin Shahbazi Feshtali, J. Sven D. Mieog, Hans Morreau, Akin Inderson, Jurjen J. Boonstra, Hans F.A. Vasen, Jeanin E. van Hooft, Bert A. Bonsing, Monique E. van Leerdam

**Collection and assembly of data:** Derk C.F. Klatte, Bas Boekestijn, Isaura S. Ibrahim, J. Sven D. Mieog, Hans Morreau, Akin Inderson, Hans F.A. Vasen, Jeanin E. van Hooft, Monique E. van Leerdam

**Data analysis and interpretation:** Derk C.F. Klatte, Bas Boekestijn, Martin N.J.M. Wasser, Shirin Shahbazi Feshtali, J. Sven D. Mieog, Saskia A.C. Luelmo, Thomas P. Potjer, Akin Inderson, Jurjen J. Boonstra, Friedo W. Dekker, Hans F.A. Vasen, Jeanin E. van Hooft, Bert A. Bonsing, Monique E. van Leerdam

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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#### **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

##### **Pancreatic Cancer Surveillance in Carriers of a Germline *CDKN2A* Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [ascopubs.org/jco/authors/author-center](http://ascopubs.org/jco/authors/author-center).

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

##### **Jeanin E. van Hooft**

**Consulting or Advisory Role:** Boston Scientific, Cook Medical, Medtronic, Olympus Medical Systems, AbbVie

No other potential conflicts of interest were reported.

## APPENDIX

### APPENDIX 1. DETAILED DESCRIPTION OF THE SURVEILLANCE PROTOCOL

Surveillance was initially offered at age 45 years, or 10 years before the youngest age of familial onset.<sup>12</sup> In 2020, following the International Cancer of the Pancreas Screening guideline,<sup>4</sup> the age of enrollment was lowered to 40 years. Before inclusion in the surveillance program, all individuals were extensively informed about the advantages and disadvantages of pancreatic cancer surveillance. Individuals with comorbidity leading to an impaired physical performance (WHO performance status 3-4), mental retardation, or a life expectancy < 5 years were excluded from surveillance.

Surveillance consisted of a dedicated magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography protocol including T1-weighted images before and after intravenous gadolinium and T2-weighted and diffusion-weighted images every 12 ± 1 months. MRI examinations were performed on a 3T system (Philips Ingenia; Philips Medical Systems, Best, the Netherlands)<sup>27</sup> and were evaluated by a highly dedicated team of abdominal radiologists (B.B., M.-N.J.M.W., and S.S.F.). Since 2012, endoscopic ultrasound (EUS) was offered optionally alternating every 6 months with MRI. EUS was performed by experienced gastroenterologists (> 1,000 procedures; A.I., J.J.B., and J.E.v.H.). During EUS, standard methods of conscious sedation (midazolam and/or fentanyl citrate or propofol) and cardiopulmonary monitoring were used.

When no abnormalities or no concerning findings (eg, minor signs of chronic pancreatitis or cysts without worrisome features) were seen, regular surveillance was continued. In the case of new or indeterminate lesions, the surveillance interval was shortened to 3 or 6 months or EUS-guided fine-needle aspiration or biopsy was performed following a standard decision protocol. If a lesion decreased or remained stable without worrisome features, the MRI surveillance interval was reset to 12 months. Worrisome features, which are suspicious lesions not warranting immediate surgery, were defined ... were defined by the most recent prevailing guideline at that time<sup>15-18</sup> and included cysts ≥ 3 cm, enhancing mural nodules < 5 mm, thickening or enhancing cyst walls, pancreatic duct dilation or abrupt changes in pancreatic duct caliber with distal pancreatic atrophy, lymphadenopathy, and a cyst growth rate ≥ 5 mm/2 years. Lesions suspicious for malignancy included mural nodules ≥ 5 mm, suspicion of main duct involvement, and cytology suspicious or positive for malignancy. Cases were discussed in a multidisciplinary team consisting of surgeons, radiologists, oncologists, pathologists, and gastroenterologists, in which a decision was made on the necessity for surgical resection.

### APPENDIX 2. DETAILED DESCRIPTION OF SECOND PANCREATIC DUCTAL ADENOCARCINOMA CASES

Five (16.1%) of 31 patients were diagnosed with a second pancreatic ductal adenocarcinoma (PDAC; Table 4). A synchronous PDAC was discovered in a patient (P18) who had undergone resection of a primary PDAC (pT3N1), 6 months earlier (previously reported in the study by Ibrahim et al).<sup>21</sup> Retrospective assessment of the preoperative magnetic resonance imaging (MRI) showed a secondary lesion in the tail for which the remaining pancreas was resected. Pathologic examination of the surgical specimen confirmed the presence of a PDAC (pT3N0, R0 resection). Four (12.9%) patients were diagnosed with metachronous PDAC 3-9 years after primary PDAC. The first patient (P6) was diagnosed with a primary cancer (pT3N0, R0 resection) at first screening (previously reported in the study by Sibinga Mulder et al).<sup>22</sup> Almost 5 years later, this patient was diagnosed with a T1aN0M0 PDAC and pancreatic intraepithelial neoplasia with high-grade dysplasia. The second patient (P22) with metachronous PDAC was previously diagnosed with stage I cancer. A second lesion was detected on MRI (pT1bN0M0, R0 resection) nearly 3.5 years later. A

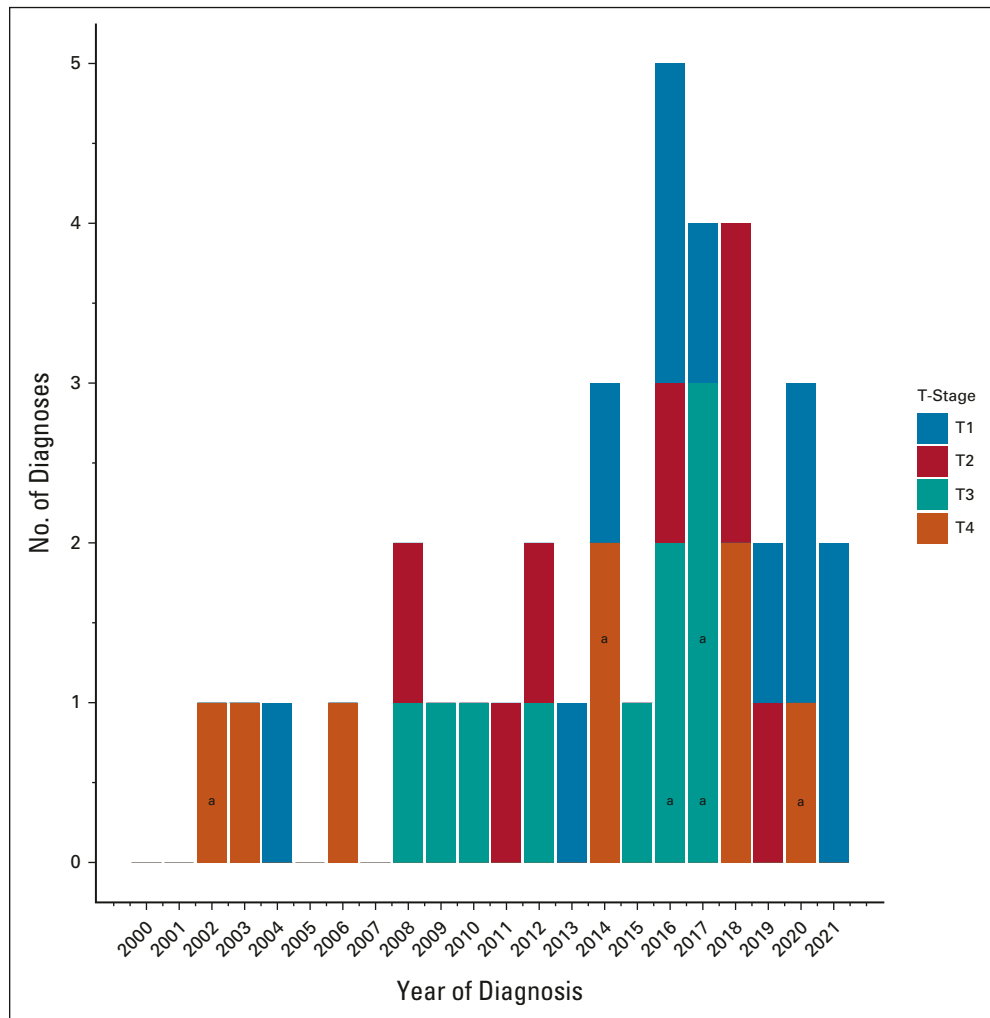
third individual participated in surveillance for 7 years when an abdominal ultrasound was performed for choledocholithiasis, in which as an incidental finding, a lesion in the pancreatic tail was discovered. This lesion was not visible on previous MRI. After distal pancreatectomy, histopathologic examination showed a stage IIA PDAC (pT3N0M0, R0 resection). Four and a half years later, a new lesion (cT2N0M0) was detected in the pancreatic head. Before pancreatoduodenectomy, she was treated with neoadjuvant chemotherapy. Histopathology showed PDAC with partial regression (ypT1cN0M0, R0 resection). Finally, a homozygous *CDKN2A* (*p16-Leiden*) pathogenic variant carrier (P10) was diagnosed at age 39 years with a primary stage III (pT2N0M0) PDAC at first screening. This patient was thereafter treated with adjuvant chemotherapy. Nine years later, a secondary malignant lesion was discovered in the remnant pancreas, for which a distal pancreatectomy was performed. This appeared a moderately differentiated stage IIB (pT1cN1M0) PDAC with tumor-positive resection margins. This patient was scheduled to receive adjuvant chemotherapy.

### APPENDIX 3. DIAGNOSTIC WORKUP OF LESIONS OTHER THAN PANCREATIC DUCTAL ADENOCARCINOMA (N = 9) DETECTED DURING SURVEILLANCE, WHICH WERE RESECTED

Nine (2.6%) of 347 individuals underwent surgery for a lesion suspected of malignancy and were found to not have pancreatic ductal adenocarcinoma. Histopathologic outcomes are provided in Appendix Table A1 (online only). The first patient (P32) had a cystic lesion in the body of the pancreas, suspicious for a side-branch intraductal papillary mucinous neoplasm (IPMN). This lesion remained stable over a period of 7 years. Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) of 2008 showed a new lesion in the pancreatic tail and growth of the side-branch IPMN in the pancreatic body. Because of suspected premalignant lesions, surgery was performed. Intraoperative ultrasound confirmed multiple intrapapillary mucinous lesions in the body, tail, and uncinete process. Subsequently, a subtotal pancreatectomy was performed. P33 was diagnosed with a lesion suspected of malignancy at first screening. MRI/MRCP showed a 10-mm hypovascular lesion in the uncinete process. Subsequent endoscopic ultrasound (EUS) and computed tomography (CT) confirmed a round hypodense lesion with a maximum diameter of 14 mm. No histologic sampling was performed. Because of a potential malignancy, a pancreatic resection was decided. P34 had three previous MRI/MRCP examinations without pancreatic abnormalities. MRI/MRCP of 2015 showed a new suspected lesion with a maximum diameter of 8 mm in the uncinete process, which was only visible on dynamic contrast-enhanced sequences. The lesion was not visualized on EUS. However, CT confirmed the presence of a 10-mm hypodense area. A pylorus-preserving pancreaticoduodenectomy was performed for a strong suspicion of malignancy. P35 underwent surveillance for more than 14 years without any pancreatic abnormalities. MRI/MRCP showed a new 11-mm focus in the pancreatic tail with a low signal intensity on T1-turbo field echo. EUS confirmed a hypodense (7 mm by 5 mm) area with an impression of a hyperechogenic center. Because of the unclear origin of the lesion and localization adjacent to the splenic artery, EUS-guided sampling was not performed. The suspicious lesion could not be confirmed with certainty on CT. A suspicion of malignancy remained on the basis of MRI findings. Therefore, a distal pancreatectomy was performed. In P36, on MRI/MRCP, a new T2 hyperintense lesion with a diffusion restriction of approximately 7 mm in the pancreatic was detected. Subsequent EUS confirmed a 5-mm hypoechogenic lesion in the pancreatic tail with a similar signal intensity as the spleen. An additional 7-mm lesion in the body was found for which histologic sampling was performed. Histopathologic evaluation concluded a grade 1 neuroendocrine tumor. An extended distal pancreatectomy was performed to resect both lesions. P37 had an 8-mm lesion in the uncinete process, which remained stable for several years. Within 2 years, this presumed side-branch IPMN increased to 19 mm. The lesion was only visible on MRI. Because of rapid growth of

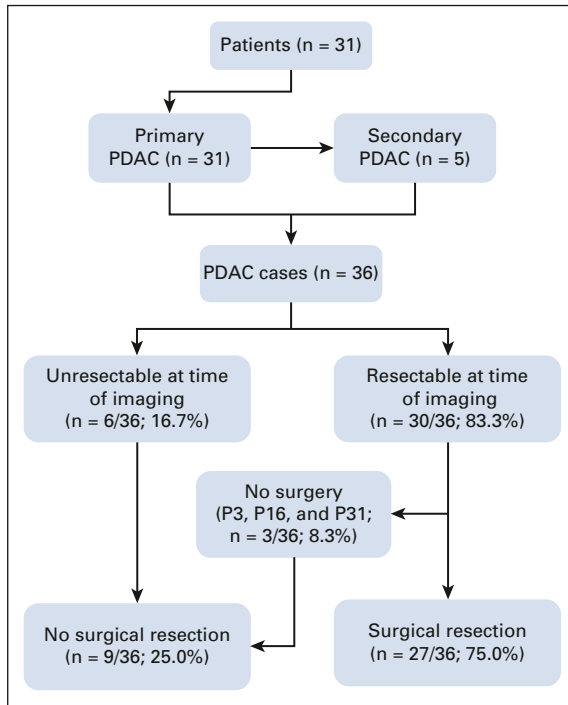
a suspected side-branch IPMN with malignant potential, a pancreatic resection was decided together with the patient. In *P38*, a small (5 mm) lesion was detected in the pancreatic tail on first MRI/MRCP. This lesion appeared hypointense on T1-turbo field echo and mildly hyperintense on T2 and showed diffusion restriction. This lesion was reproducible on EUS, on which a hypoechogenic lesion of 6 mm was observed. Unfortunately, there was no safe window for EUS-guided sampling. Because of a suspected malignancy on the basis of imaging findings, a pancreatic resection was performed. *P39* underwent surveillance alternating MRI and EUS. Previous MRI did not show any abnormalities. On EUS, a hypoechogenic lesion of 28 × 30 mm was found in the pancreatic tail, for which a fine-needle biopsy was performed. Immunohistochemical staining was positive

for glucagon and insulin. Differential diagnosis of a grade 1 neuroendocrine tumor (Ki-67 index: 1%-2%) or diffuse islet cell hyperplasia was observed. Subsequent MRI confirmed the presence of a 10-mm hypointense lesion with delayed contrast enhancement. This lesion could not be confirmed on CT. Surgery was chosen on the basis of lesion growth and the potential of a neuroendocrine tumor. Finally, *P40* had two previous MRI examinations without abnormalities when an increase of the main pancreatic duct diameter was observed from 5 mm to 7 mm up to the ampulla. EUS confirmed a dilated pancreatic duct and showed an enlarged ampullary region, of which biopsies were taken. Histopathology showed adenocarcinoma, for which a pylorus-preserving pancreaticoduodenectomy was performed.

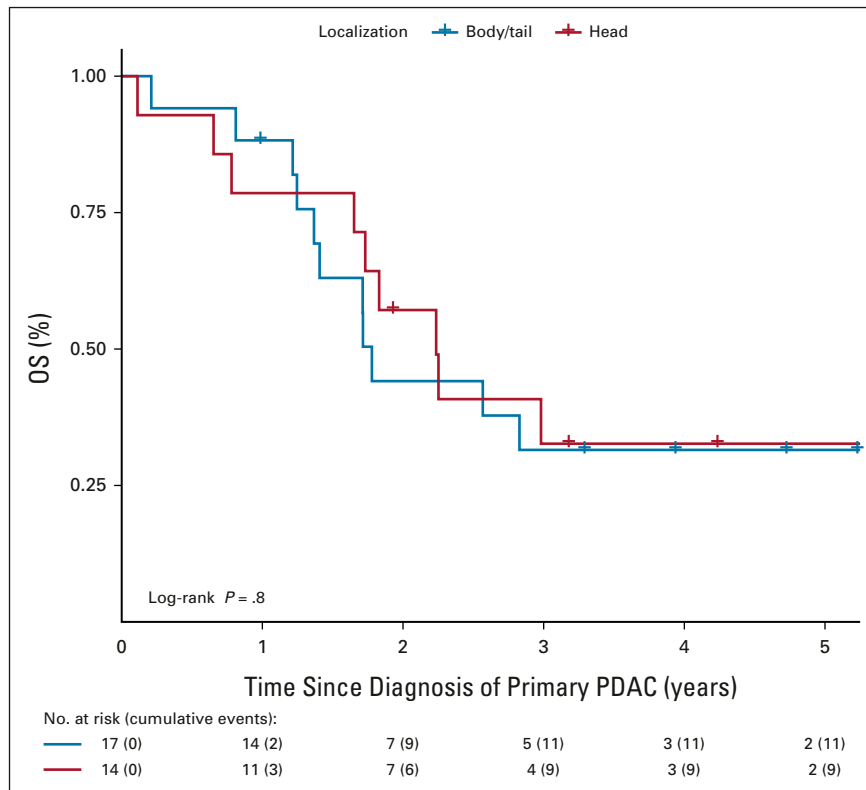


**FIG A1.** Number of diagnoses (total  $n = 36$ ) stratified by T-stage per year during 20 years of surveillance. <sup>a</sup>Cases are patients who presented with interval cancers, which were not detected through screening. T-stage, tumor stage.





**FIG A2.** Flowchart of management of 36 cases of PDAC in 31 patients who were diagnosed with PDAC ( $n = 31$ ). Five of 31 patients were diagnosed with a second PDAC. Three patients with resectable disease at the time of diagnosis did not undergo surgery (Table 3). P3 had a concomitant melanoma metastasis and did therefore not have surgery. P16 refused to undergo surgery. P31 decided to undergo an alternative treatment with transarterial chemoembolization and microwave ablation, which was not advised by our multidisciplinary team. P, patient; PDAC, pancreatic ductal adenocarcinoma.



**FIG A3.** Kaplan-Meier curves for OS of *CDKN2A* pathogenic variant carriers after diagnosis of primary PDAC ( $n = 31$ ) stratified by localization in the head ( $n = 14$ ) versus body or tail ( $n = 17$ ). OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

**TABLE A1.** Details of Patients With Lesions Other Than Pancreatic Ductal Adenocarcinoma (n = 9) Detected During Surveillance Who Underwent Pancreatic Surgery

No.	Diagnosis Year	Age at Diagnosis, years/Sex	Follow-Up Duration, months	Prior Screening Modality	Time Since Previous Screening, months	Detection Modality	Interval Cancer	Management	Cytologic or Histopathologic Results	TNM Stage	Outcome/Survival Time From Diagnosis, months
<i>P32</i>	2008	62/F	87	MRI/MRCP	4	MRI/MRCP	—	DP	Multifocal PanIN with low-grade dysplasia and extensive multifocal pancreatitis		Alive/162
<i>P33</i>	2014	66/F	4	—	—	MRI/MRCP	—	PPPD	Gastric type IPMN with low-grade dysplasia		Alive/93
<i>P34</i>	2015	55/M	43	MRI/MRCP	12	MRI/MRCP	—	PPPD	Ductal proliferation with chronic inflammation and islets of Langerhans hyperplasia	—	Alive/76
<i>P35</i>	2016	65/M	170	MRI/MRCP	12	MRI/MRCP	—	DP + wedge excision of gastric lesion	Focal PanIN with low-grade dysplasia + gastric stromal tumor	—	Alive/60
<i>P36</i>	2017	54/F	30	MRI/MRCP	14	MRI/MRCP	—	DP	Grade 1 neuroendocrine tumor of 4 mm, neuroendocrine adenosis with microadenomas, multifocal PanIN with low-grade dysplasia	pT1NOM0	Alive/46
<i>P37</i>	2017	63/F	107	EUS	6	MRI/MRCP	—	PPPD	IPMN with low-grade dysplasia	—	Alive/44
<i>P38</i>	2018	47/F	4	—	—	MRI/MRCP	—	DP	Ductal proliferation, PanIN with low-grade dysplasia		Alive/36
<i>P39</i>	2019	58/M	51	MRI/MRCP	11	EUS	—	DP	Diffuse islet cell hyperplasia	—	Alive/28
<i>P40</i>	2019	49/M	33	MRI/MRCP	14	MRI/MRCP	No	PPPD	Moderately differentiated ampullary carcinoma, R0 resection	pT1aNOM0	Alive/22

NOTE. Patient numbers (No.) in italics were reported in previous publications

Abbreviations: DP, distal pancreatectomy; EUS, endoscopic ultrasound; F, female; IPMN, intraductal papillary mucinous neoplasm; M, male; MRI/MRCP, magnetic resonance imaging with magnetic resonance cholangiopancreatography; PanIN, pancreatic intraepithelial neoplasia; PPPD, pylorus-preserving pancreaticoduodenectomy.