Early detection of pancreatic cancer in high-risk individuals

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Surveillance for Pancreatic Cancer in High-Risk Individuals Leads to Improved Outcomes: A Propensity-Score Matched Analysis

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ABSTRACT

Background & aims

Recent pancreatic cancer surveillance programs of high-risk individuals have reported improved outcomes. This study assessed to what extent outcomes of pancreatic ductal adenocarcinoma (PDAC) in patients with a *CDKN2A/p16* pathogenic variant diagnosed under surveillance are better as compared with patients with PDAC diagnosed outside surveillance.

Methods

In a propensity score matched cohort using data from the Netherlands Cancer Registry, we compared resectability, stage and survival between patients diagnosed under surveillance with non-surveillance patients with PDAC. Survival analyses were adjusted for potential effects of lead time.

Results

Between January 2000 and December 2020, 43,762 patients with PDAC were identified from the Netherlands Cancer Registry. Thirty-one patients with PDAC under surveillance were matched in a 1:5 ratio with 155 non-surveillance patients based on age at diagnosis, sex, year of diagnosis, and tumor location. Outside surveillance, 5.8% of the patients had stage I cancer, as compared with 38.7% of surveillance patients with PDAC (Odds ratio [OR], 0.09; 95% confidence interval [CI], 0.04-0.19). In total, 18.7% of non-surveillance patients vs 71.0% of surveillance patients underwent a surgical resection (OR 10.62; 95% CI, 4.56 – 26.63). Patients in surveillance had a better prognosis, reflected by a 5-year survival of 32.4% and a median overall survival of 26.8 months vs 4.3% 5-year survival and 5.2 months median overall survival in non-surveillance patients (hazard ratio, 0.31; 95% CI 0.19-0.50). For all adjusted lead times, survival remained significantly longer in surveillance patients than in non-surveillance patients.

Conclusion

Surveillance for PDAC in carriers of a *CDKN2A/p16* pathogenic variant results in earlier detection, increased resectability, and improved survival as compared with non-surveillance patients with PDAC.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has the worst outcomes of all cancers and it is soon expected to become the second-leading cause of cancer-related mortality.[1] Most patients have either locally advanced, unresectable disease or distant metastasis at presentation, which stresses the urgent need for early detection.[2] Cancer screening can contribute to decreasing cancer mortality and morbidity through either the detection of precursor lesions or early invasive tumors. Unfortunately, population-wide pancreatic screening programs are presently not viable due to the relatively low incidence of PDAC and absence of a reliable screening test applicable for mass screening.[3] Instead, pancreatic surveillance programs focus on subgroups of patients with a high risk of developing PDAC.

Individuals eligible for participation in pancreatic surveillance programs are carriers of germline pathogenic variants (PVs) in PDAC susceptibility genes or a strong family history.[4] Lifetime risk estimates for PDAC for these high-risk individuals (HRIs) vary from 2% for *BRCA1* to more than 30% for Peutz-Jeghers syndrome.[5] Guidelines advocate offering annual imaging to certain HRIs by either magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), or a combination of both.[4, 6] To consider a pancreatic surveillance program to be beneficial, it should result in a reduction of mortality and prolonged survival. So far, studies evaluating the outcomes of surveillance have shown conflicting results. Whereas most programs were insufficiently able to substantially impact disease course, some centers reported successful treatment of early-stage PDAC or high-grade precursor lesions.[7-10] Recently, our group reported on the yield and outcomes of 20 years of pancreatic surveillance in a large cohort of germline *CDKN2A/p16* PV carriers.[11] We observed a 5-year overall survival (OS) rate of 32%, which seems notably better than the survival outcomes (5%-10%) of patients with PDAC within the general population. However, possible differences in patient characteristics and the potential influence of lead-time bias should be taken into account when making a direct comparison of outcomes.

Ideally, to provide more evidence on surveillance being beneficial, PDAC outcomes should be compared with control groups of HRIs not participating in surveillance. Unfortunately, sufficiently large control groups with long follow-up duration are not available, and there are ethical concerns in withholding HRIs from surveillance in a (randomized) trial setting. As an alternative, comparison with a control group of patients with PDAC with similar characteristics from within the general population might provide valuable insight if outcomes of PDAC diagnosed in surveillance do have better outcomes.

Therefore, in this current study we evaluated to what extent pancreatic cancer surveillance resulted in a stage-shift, improved resectability, and lead-time adjusted survival of PDAC, in a high-risk cohort of germline *CDKN2A/p16* PV carriers as compared with patients diagnosed outside surveillance, in the general population.

METHODS

Data Sources

Pancreatic Surveillance Program Registry

The Leiden University Medical Center has organized a pancreatic surveillance program for carriers of a proven pathogenic or likely pathogenic *CDKN2A/p16* variant. The vast majority (99%) of this population carries a specific Dutch founder PV in *CDKN2A* known as *CDKN2A/p16-Leiden* (c.225_243del19). From 2000 to 2022, 347 individuals have participated in the program. A detailed description of the surveillance protocol and outcomes can be found in a recent pubication.[11] In short, surveillance was offered at a starting age of 45 years, or 10 years before the youngest age of familial onset. In 2020, following the International Cancer of the Pancreas Screening Consortium (CAPS) Guideline, the age of enrollment was lowered to 40 years.[4] Imaging was performed using MRI/magnetic resonance cholangiopancreatography every 12 months, and since 2012, EUS was offered optional alternating every 6 months with MRI. Thus, individuals alternating MRI and EUS surveillance (19.8% of the surveillance cohort) underwent screening every 6 months. From the surveillance registry, we selected all patients who were diagnosed with primary PDAC since 2000. All participants provided written informed consent before enrolment in the surveillance program. This study was approved by the institutional review board of the Leiden University Medical Center (MEC P00.107; P21.006) and was registered at the Netherlands Trial Register (NL9158).

Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) records data on all patients with newly diagnosed cancer in the Netherlands, covering more than 17 million inhabitants. Completeness of the NCR is estimated to be at least 95%. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O).[12] Tumor location, histology, and stage are registered by trained data managers according to the ICD-O (ICD-O-3). Tumors were coded according to the Union for International Cancer Control TNM classification valid at the time of diagnosis. Stage was based on pathology (pTNM) when histopathology was available. If not, clinical stage (cTNM) was selected. Survival data was obtained through annual linkage to the Dutch Personal Records Database. The study was approved by the NCR review board and the scientific committee of the Dutch Pancreatic Cancer Group.

Study Population and Data Collection

All patients diagnosed with PDAC (ICD-O C25, excluding C25.4) between January 1st, 2000 and December 31st, 2020, were identified from the NCR and included in this study (source population). Exclusion criteria were incidental diagnoses at autopsy, diagnosis or cancer treatment abroad, or younger than 18 years at diagnosis. From the source population, we identified all patients with primary PDAC who were enrolled in the LUMC pancreatic surveillance program using their patient identification number. These cases were labeled as PDAC cases diagnosed under surveillance.

Statistical Analysis

A propensity score matched cohort was constructed to compare patients from the general population with primary PDAC diagnosed outside surveillance with carriers of a germline *CDKN2A/p16* mutation who were diagnosed with PDAC under surveillance (henceforth referred to as *non-surveillance patients* and *surveillance patients*, respectively.[13] Propensity scores were estimated using multivariable logistic regression including characteristics of age at diagnosis, sex, year of diagnosis (in 5-year strata), and tumor location (head vs. body or tail). Because to the large number of missing data, other variables such as body mass index and performance status could not be included in the matching procedure. We considered administration of neoadjuvant chemotherapy related to the study outcomes and was therefore not included. Matching was performed in a 1:5 ratio using nearest neighbor matching without replacement, with a caliper width of 0.2 SD, using the MatchIt package in R.[14] Balance of matching variables was assessed by the standardized mean difference (SMD), for which an SMD <0.1 was considered an adequate balance.

Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range, depending on the distribution, and categorical variables as frequencies and percentage of total. Two-sample independent t-test and Mann-Whitney U test were used to compare normally and non-normally distributed variables, respectively. (Ordinal) logistic regression was used to study the association between non-surveillance- and surveillance-detected PDAC with stage and resectability..

Survival Analysis and Adjustment for Lead Time

In the propensity score matched cohort, Kaplan-Meier survival analysis was used to estimate OS after the date of PDAC diagnosis and the log-rank test was used to compare survival between groups. Survival was subsequently adjusted for potential lead-time bias. Lead-time bias occurs when a cancer is detected by screening earlier than that it would have been diagnosed because of symptoms, without affecting the disease course, thereby resulting in apparent extended survival. To estimate lead time for the surveillance group, we used the approach described by *Duffy et al.*.[15]. The time for an undetected cancer to become symptomatic is defined as the sojourn time (κ), which is a measure of how much diagnosis may be advanced by screening. Currently, there are no reports on estimations for lead time in surveillance for PDAC available. Therefore, to estimate the lead time, we arbitrarily selected fixed sojourn times of 3, 6, 12, and 15 months. This was based on previous literature estimating that progression from stage I to stage IV has an average duration of 15 months.[16] The expected additional follow-up time due to lead time was then computed and subtracted from the observed survival time since diagnosis of PDAC detected through surveillance (ie, screen-detected tumors). Interval cancers were included in survival analysis, although these were not adjusted for lead time. Prevalent cancers (ie, detected during the first screening examination) were included in survival analysis and adjusted for lead time. Vital status (survival) was evaluated until February 1, 2022. All statistical analyses were performed using R version 4.2.2.

RESULTS

From the NCR, 43,762 patients with PDAC were identified. This included 31 patients who were diagnosed in the pancreatic cancer surveillance cohort. In the unmatched cohort, the median age at diagnosis was 71 (interquartile [IQR], 63-78) years for non-surveillance and 60 (53 – 64) years for surveillance patients, respectively. All surveillance cases were participating in annual MRI surveillance. Cases detected through screening were diagnosed with MRI and five (16.1%) out of 31 patients presented with interval cancers, which were not diagnosed during annual screening examinations. Eight (25.8%; 8 of 31) PDACs were classified as prevalent as they were detected at first screening.

The 1-, 3-, and 5-year age-adjusted relative survival rates in the total unmatched cohort were 20.8% (95% confidence interval [CI], 20.3%-21.2%), 5.5% (95% CI, 5.2%-5.8%), and 3.3% (95% CI, 3.0%-3.5%), respectively. Due to the small sample size, age-adjusted relative survival could not be calculated separately for surveillance patients.

From the source population, all 31 patients with PDAC diagnosed in pancreatic cancer surveillance were matched in a 1:5 ratio with 155 non-surveillance patients with PDAC. Matching covariates (age, sex, year of diagnosis, and tumor location) appeared well balanced between groups (SMD <0.01). Details of the study population before and after propensity score matching are provided in **Table 1**.

Outcomes in the Propensity Score-Matched Cohort

Non-surveillance patients were diagnosed with stage I disease in 5.8% (9 of 155) of the cases, compared to 38.7% (12 of 31) of surveillance patients (odds ratio, 0.09; 95% CI, 0.04-0.19; **Figure 1A**). Most (61.3%; 95 of 155) of non-surveillance patients were diagnosed with stage IV disease compared with 9.7% (3 of 31) of surveillance patients. Non-surveillance patients underwent surgical resection in 18.7% (29 of 155) of the cases, as compared with 71.0% (22 of 31) of surveillance patients (odds ratio, 10.62; 95% CI, 4.56-26.63); **Figure 1B**).

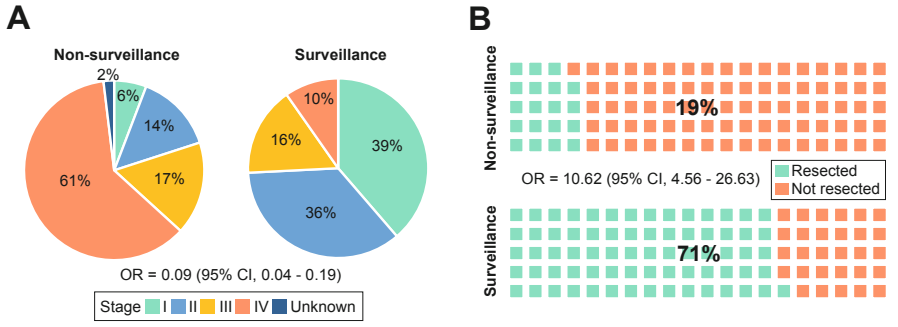


Figure 1. PDAC Stage (*A*) and resectability (*B*) of non-surveillance patients (n = 155) compared with surveillance patients (n = 31), after propensity score matching. OR, odds ratio.

Table 1. Patient Characteristics, and Tumor and Treatment Characteristics Before and After Propensity Score Matching

	Unmatched cohorts			Matched cohorts		
Patient characteristics	**Non-surveillance (n = 43,731)**	**Surveillance (n = 31)**	**SMD**	**Non-surveillance (n = 155)**	**Surveillance (n = 31)**	**SMD**
Age at diagnosis, median (IQR)	71 (63–78)	60 (53–64)	-1.4	60 (10.5)	60 (9.0)	0.0
<40	209 (0.5)	1 (3.2)		2 (1.3)	1 (3.2)	
40–49	1509 (3.5)	4 (12.9)		19 (12.3)	4 (12.9)	
50–59	5744 (13.1)	10 (32.3)		54 (34.8)	10 (32.3)	
60–69	11 973 (27.4)	13 (41.9)		65 (41.9)	13 (41.9)	
70–79	14 818 (33.9)	3 (9.7)		15 (9.7)	3 (9.7)	
≥80	9 478 (21.7)	0 (0.0)		0 (0.0	0 (0.0)	
Male	21 972 (50.2)	11 (35.5)	0.3	52 (33.5)	11 (35.5)	0.0
Year of diagnosis						
2000–2005	9 125 (20.9)	3 (9.7)	-0.4	16 (10.3)	3 (9.7)	0.0
2006–2010	9 628 (22.0)	5 (16.1)	-0.2	24 (15.5)	5 (16.1)	0.0
2011–2015	11 366 (26.0)	6 (19.4)	-0.2	26 (16.8)	6 (19.4)	0.0
2016–2020	13 612 (31.1)	17 (54.8)	0.5	89 (57.4)	17 (54.8)	0.0
Tumor and treatment characteristics						
Tumor location						
Head	26 586 (60.8)	15 (48.4)	-0.2	75 (48.4)	15 (48.4)	0.0
Body/tail	11 286 (25.8)	13 (41.9)	0.5	80 (51.6)	16 (51.6)	0.0
Other	3 223 (7.4)	3 (9.7)	-0.3	13 (8.4)	0 (0.0)	0.0
Unknown	2 634 (6.0)	0 (0.0)	-0.3	6 (3.9)	0 (0.0)	0.0
Surgical resection	5 694 (13.0)	22 (71.0)	—	29 (18.7)	22 (71.0)	—

Table 1. Continued.

	Unmatched cohorts			Matched cohorts		
Patient characteristics	**Non-surveillance (n = 43,731)**	**Surveillance (n = 31)**	**SMD**	**Non-surveillance (n = 155)**	**Surveillance (n = 31)**	**SMD**
Whipple/PPPD/PRPD	4 556 (80.0)	12 (54.5)		19 (65.5)	12 (54.5)	
Distal pancreatectomy	665 (11.7)	9 (40.9)		8 (27.6)	9 (40.9)	
Total pancreatectomy	92 (1.6)	0 (0.0)		0 (0.0)	0 (0.0)	
Other type or unspecified	381 (6.7)	1 (4.5)		2 (6.9)	1 (4.5)	
Neoadjuvant chemotherapy	641 (1.5)	3 (9.7)	—	6 (3.9)	3 (9.7)	—

NOTE. Numbers are n (%), unless stated otherwise.
IQR, interquartile range; PPPD, pylorus preserving pancreaticoduodenectomy; PRPD, pylorus-resecting pancreatoduodenectomy.

The mortality rate (ie, the number of deaths per unit of follow-up duration) per 100 person-years was 114.5 (95% CI, 96.2-135.3) in non-surveillance patients and 21.9 (95% CI, 13.4-33.8) in surveillance patients (**Table 2**). In survival analysis unadjusted for lead time, median OS was more than 5 times higher in surveillance vs non-surveillance patients (26.8 months vs 5.2 months; hazard ratio, 0.22; 95% CI, 0.14-0.36; **Supplementary Figure 1**). This corresponded to a 5-year survival rate of 4.3% (95% CI, 0.9% – 20.1%) in non-surveillance patients and 32.4% (95% CI, 19.1 – 54.9) in surveillance patients.

Table 2. Summary of Survival Outcomes in Non-Surveillance Patients (n = 155) Compared With Patients Diagnosed Under Surveillance (n = 31), After Propensity Score Matching, Unadjusted and Adjusted for Lead Time With Different Assumptions Regarding the Mean Sojourn Time (κ = 3 months; κ = 6 months; κ = 12 months; κ = 15 months)

Survival outcomes	Non-surveillance (n = 155)	Surveillance (n = 31)			
Unadjusted for lead time					
Number of deaths (%)	138 (89.0)	20 (64.5)			
Mortality rate (95% CI)[a]	114.5 (96.2–135.3)	21.9 (13.4–33.8)			
Median OS (95% CI), mo	5.2 (3.8–6.6)	26.8 (20.6–NA)			
Survival rate (95% CI)					
1-year	26.5% (20.2%–34.4%)	83.9% (71.9%–97.9%)			
3-year	8.6% (4.5%–16.7%)	32.4% (19.1%–54.9%)			
5-year	4.3% (0.9%–20.1%)	32.4% (19.1%–54.9%)			
Hazard ratio (95% CI)	Reference	0.31 (0.19–0.50)			
Adjusted for lead time	—	κ = 3 months	κ = 6 months	κ = 12 months	κ = 15 months
Median OS (95% CI), mo	5.2 (3.8–6.6)	23.9 (17.6–NA)	22.0 (15.2–NA)	19.7 (11.4–NA)	15.2 (10.0–NA)
5-year survival rate (95% CI)	4.3% (0.9%–20.1%)	32.4% (19.1%–54.9%)	32.3% (19.0%–54.8%)	32.3% (19.0%–54.8%)	32.1% (18.9%–54.7%)
Hazard ratio (95% CI)	Reference	0.34 (0.21–0.55)	0.37 (0.23–0.60)	0.45 (0.28–0.73)	0.43 (0.27–0.69)

k, sojourn time; mo, months; NA, not available (upper limit of 95% CI could not be estimated due to a low number of events).
[a]Per 100 person-years.

Lead-Time Adjusted Survival

Survival in the surveillance group was subsequently adjusted for lead time with assumed sojourn times of 3, 6, 12, and 15 months. The corresponding computed lead times are provided in **Supplementary Table 1**. Survival remained unadjusted in patients with interval cancers. Following lead-time adjustment in surveillance patients, estimated median OS ranged from 23.9 (95% CI, 17.6 – NA) months for 3 months sojourn time, to 15.2 (95% CI, 10.0 – NA) months for 15 months sojourn time (**Table 2** and **Figure 2**), in comparison with a median OS of 5.2 (95% CI, 3.8-6.6) months in non-surveillance patients. The 5-year survival rate in patients under surveillance remained above 32%. For all assumed sojourn times, survival remained significantly longer in surveillance patients as compared with non-surveillance patients: hazard ratio, 0.43 (95% CI, 0.27 – 0.69) for non-surveillance vs. surveillance patients, adjusted for 15 months sojourn time.

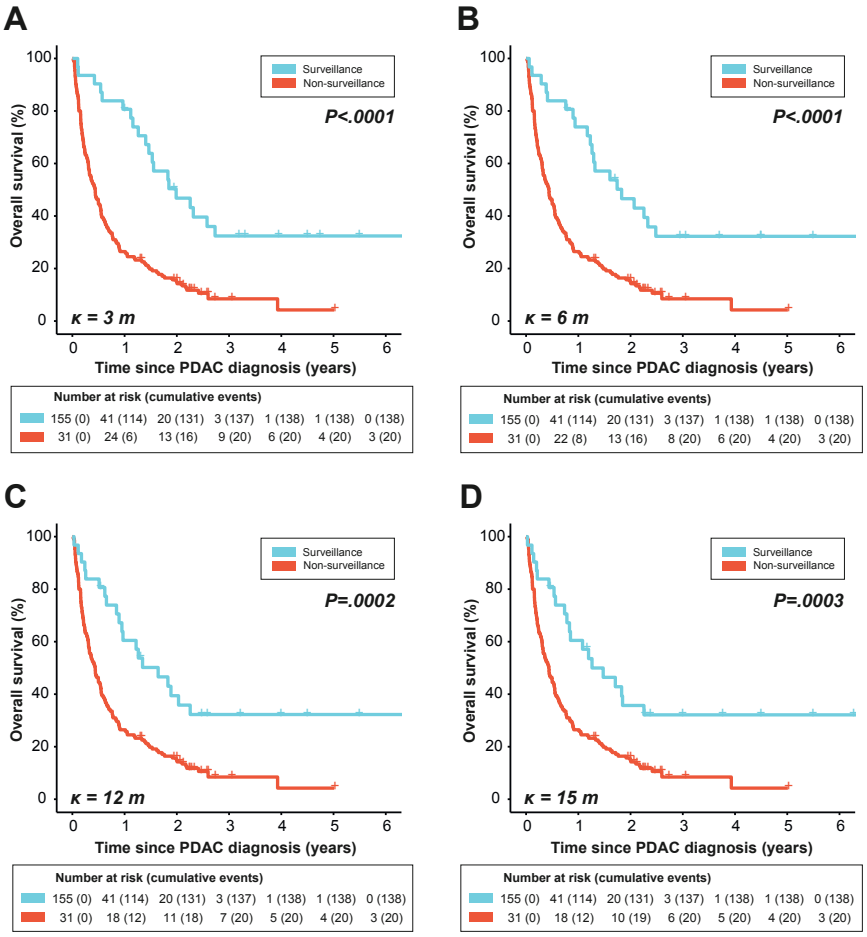


Figure 2. Kaplan-Meier curves for lead-time adjusted OS after diagnosis of PDAC in non-surveillance (n = 155; *red*) and surveillance (n = 31; *blue*) patients, after propensity score matching, with different assumptions regarding the mean sojourn time (*A*: κ = 3 months; *B*: κ = 6 months; *C*: κ = 12 months; *D*: κ = 15 months). κ = sojourn time.

Subgroup Analyses

In patients who underwent resection, median OS was 26.1 (95% CI, 19.8-NA) months in non-surveillance patients and 33.9 (95% CI, 25.2-NA) months in surveillance patients unadjusted for lead time ($P < .0001$; **Supplementary Figure 2A** and **2B**). When adjusted for a sojourn time of 12 months, median OS was 22.7 (95% CI, 16.1-NA) months in surveillance patients who underwent resection ($P = .0007$; **Supplementary Figure 2C**). Five-year survival of those diagnosed with stage II, III, or IV disease was 3.3% (95% CI, 0.7%-15.9%) in non-surveillance and 15.8% (95% CI, 5.6-44.6) in surveillance patients (**Supplementary Table 2** and **Supplementary Figure 3A** and **3B**). This remained unchanged when adjusted for a sojourn time of 12 months (**Supplementary Figure 3C**).

DISCUSSION

This study demonstrated that outcomes of PDAC in HRIs carrying a germline *CDKN2A/p16* PV participating in a pancreatic surveillance program are notably better than patients who are diagnosed in the general population. The surgical resection rate was almost 4 times higher in the surveillance group and they were more often diagnosed with stage I cancer (39% vs. 6%), resulting in a far more favorable prognosis with a median OS of 26.8 months vs. 5.2 months in non-surveillance patients. The finding of improved prognosis persisted when survival was adjusted for lead time for different assumptions of sojourn times.

In recent years, multiple prospective studies on pancreatic cancer surveillance in HRI have shown detection of early stage PDAC with improved outcomes.[10, 11, 17] Based on these findings, multiple consortia and societies, such as the CAPS consortium, the American Society for Gastrointestinal Endoscopy, and American Society of Clinical Oncology have published guidelines recommending offering surveillance in expert centers with evaluation of the yield and outcomes.[4 18, 19] However, a concern is that in absence of sufficiently large control groups with unscreened controls, improved outcomes are largely explained by lead-time bias. This study is the first pancreatic surveillance report to adjust for lead-time bias. Even when assuming that diagnosis by surveillance was more than a year before diagnosis by symptoms, survival outcomes remained superior for those diagnosed under surveillance. Although the outcomes presented here are encouraging and endorses our earlier findings[11], a significant proportion of surveillance patients (61%) still had poor outcomes because of diagnosis in a late stage (T2–4N0M0 and nodal or distant metastatic PDAC), with a 5-year survival of 16%. A recent meta-analysis[9] including 13 studies of 2169 HRIs showed that in surveillance programs, late-stage cancers constituted a considerable proportion (58.5%) of PDACs. The authors posed surveillance nonadherence and delay as important contributors to late-stage PDACs, which underlines the importance of registries with an active follow-up. In addition, surveillance currently solely relies on imaging, which has proven to be suboptimal. Imaging features associated with neoplastic progression are difficult to characterize or may be masked by chronic pancreatitis, which may result in false-negative findings. Moreover, a subset of lesions appears to progress to advanced disease before the next annual screening.[20] The application of artificial intelligence could offer a powerful tool to mitigate these diagnostic errors.[21] Complementary to imaging, biomarkers in blood or pancreatic juice could have a major impact in our abilities to distinguish low-grade lesions from high-grade dysplasia or early invasive cancer.[22-24]

A recent report of the multicenter Cancer of the Pancreas Screening-5 (CAPS5) study showed diagnosis of stage I in 77.8% of screen-detected PDACs, with a median survival of 9.8 years.[10] These outcomes are superior to those presented in this current study. However, CAPS5 constitutes a mixed cohort of various germline PV carriers and familial pancreatic cancer kindreds, whereas the observed outcomes of surveillance reported in this study were based on a homogenous cohort constituting of *CDKN2A/p16* germline PV carriers only. *CDKN2A/p16* germline PV carriers are amongst the highest risk, as eventually 1 in 4 will develop PDAC,[11] compared to up to one in 10 for most other hereditary cancer syndromes associated with PDAC.[5] Moreover, it is suggested that CDKN2A/p16 germline PV carriers have a particularly aggressive cancer progression,[10] which could partially explain the discrepancy in outcomes between CAPS5 and this present study. The potentially more aggressive

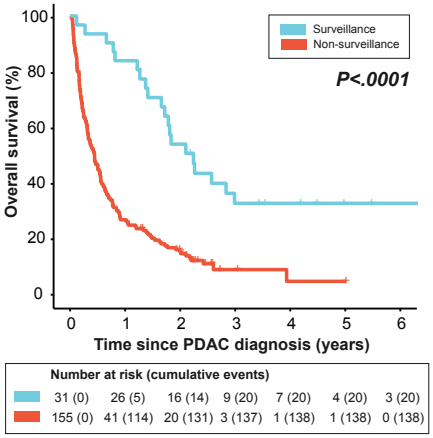
nature is also reflected by the fact that patients diagnosed under surveillance were on average 10 years younger than patients with non-surveillance PDAC. Currently, it is not yet established whether PDACs in a setting of *CDKN2A/p16* germline PVs differ in biology, although in an earlier study we showed that these carriers are at a significant risk of a second PDAC.[11] Moreover, in other forms of cancer, early onset of disease is associated with a more aggressive phenotype.[25, 26] Future studies should elucidate the primary drivers of pancreatic malignancy in various hereditary cancer syndromes, which could improve clinical management of these HRIs.

Literature shows that in the general population most PDACs occur in the head, while it is estimated that 20% to 25% originate in the body/tail.[27, 28] Our data are consistent that in a quarter of non-surveillance patients a tumor was found in the body/tail. However, this proportion was larger in surveillance patients (41.9%), which again could be because of differences in tumor biology, which needs further elucidation.[29]

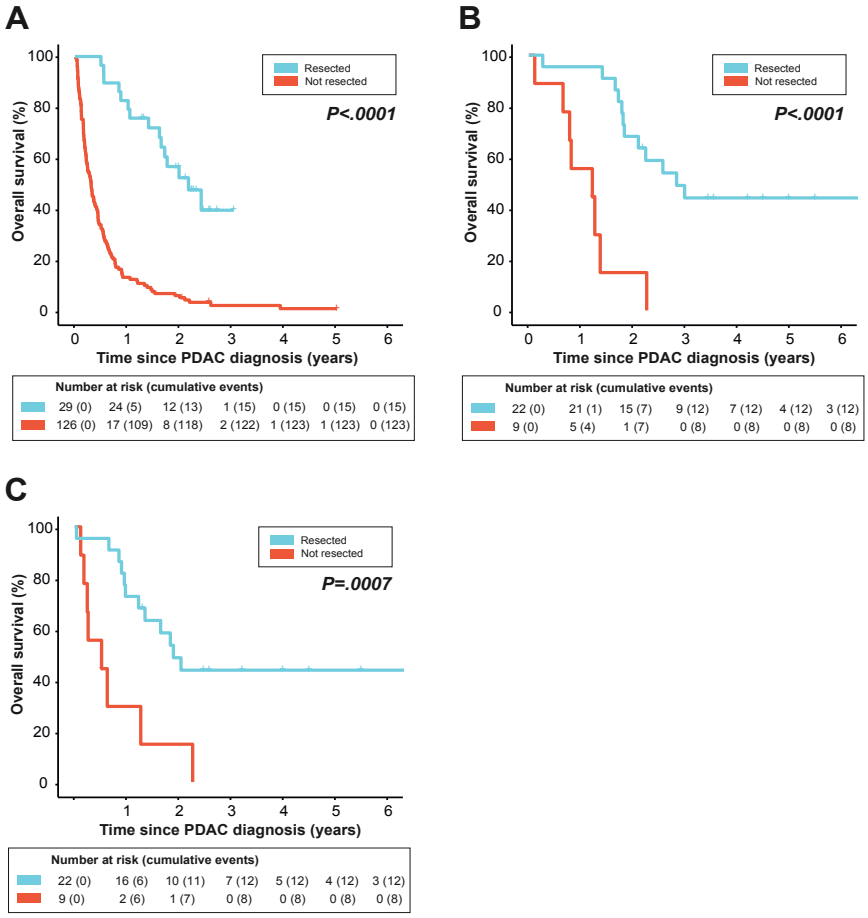
There are a few limitations to our study. First, although the NCR is considered an accurate registry regarding cancer diagnosis,[30] data on characteristics such as body mass index and comorbidities were incomplete, limiting more extensive matching. It is therefore likely that our findings are still influenced by unmeasured confounders, which is inherent by the observational nature of our study. For instance, the surveillance group may overall be a more health-conscious population with a better functional status, which perhaps may have contributed to better outcomes. Second, it is important to emphasize that this study compared a highly selected group of individuals with a germline *CDKN2A/p16* PV with individuals from the general population, of whom the potential presence of germline mutations was unknown. As noted previously, PDACs of these germline PV carriers likely have a different tumor biology, which may also influence prognosis. However, based on our earlier observations and as suggested by Dbouk et al.,[10] PDACs in carriers of a germline *CDKN2A/p16* PV appear to have more aggressive disease, which likely results in an underestimation of a surveillance benefit.[11] Ideally, to further strengthen the evidence on a benefit of surveillance in this cohort, our findings should be compared with a sufficiently large control group of individuals with a germline *CDKN2A/p16* PV not under surveillance. Third, possibly, a small number of patients from the general population (non-surveillance group) were also diagnosed due to surveillance of high-risk features (eg, familial pancreatic cancer, germline PVs, or pancreatic cyst surveillance). However, this would again most likely result in an underestimation of the benefits observed in this study. Fourth, we currently have limited data on patients with PDAC diagnosed under surveillance with long-term follow-up. Long-term survival (> 5 years) is less influenced by lead time and will therefore give an even more accurate representation of a survival benefit. Fifth, although patients were matched on year of diagnosis, the 20-year study period overall does not provide an accurate representation of the current prognosis of pancreatic cancer, which has slightly improved over time.[31] Lastly, the relatively small number of patients with PDAC in the surveillance group has restrained us from conducting extensive subgroup analysis, such as stratifying survival per pancreatic cancer stage.

In conclusion, in this study, we show that surveillance for PDAC in HRIs results in significant earlier detection, increased resectability, and improved survival as compared with average-risk individuals diagnosed with PDAC not under surveillance. This reaffirms that pancreatic surveillance for certain HRIs is beneficial and could have a meaningful impact on disease course. Future efforts should focus on enhancing our diagnostic capabilities by artificial intelligence, and discovery of biomarkers.

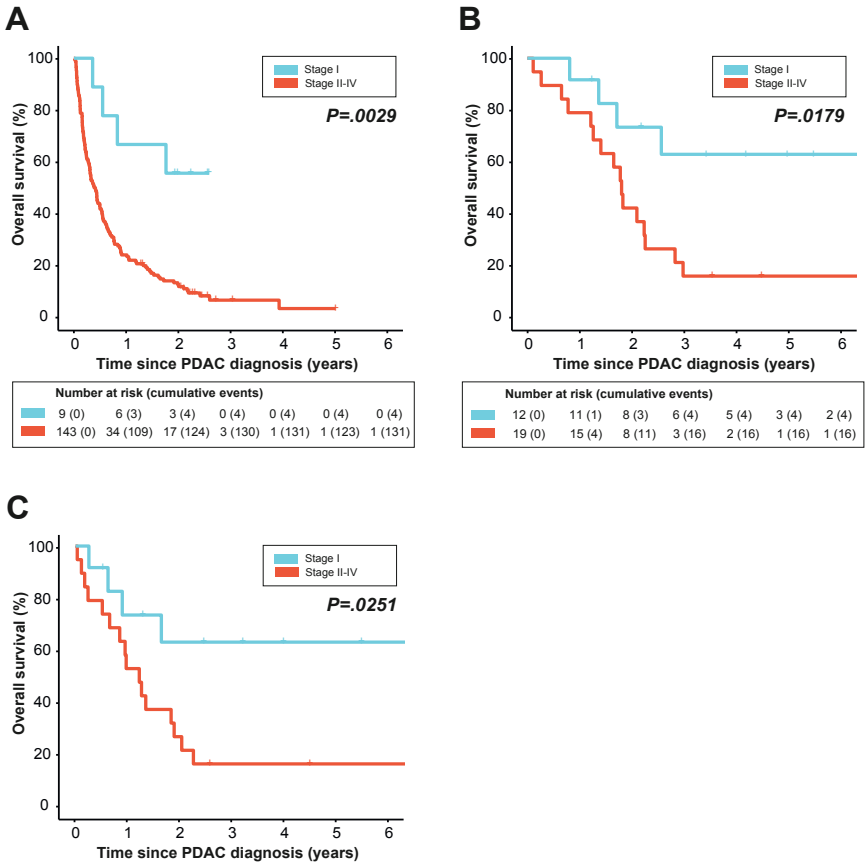
SUPPLEMENTARY MATERIALS



Supplementary Figure 1. Kaplan-Meier curve for OS after diagnosis of PDAC in non-surveillance (n = 155; *red*) and surveillance (n = 31; *blue*) patients, after propensity score matching, without adjustment for lead time.



Supplementary Figure 2. Kaplan-Meier curve for OS by PDAC that was resected (*blue*) vs not resected (*red*), after propensity score matching: (*A*) non-surveillance patients (n = 155), (*B*) surveillance patients (n = 31) without lead time adjustment, and (*C*) surveillance patients (n = 31) with lead time adjustment assuming a mean sojourn time of 12 months.



Supplementary Figure 3. Kaplan-Meier curve for OS by stage I (*blue*) vs stage II–IV (*red*), after propensity score matching: (*A*) non-surveillance patients (n = 155), (*B*) surveillance patients without lead time adjustment, and (*C*) surveillance patients (n = 31) with lead time adjustment assuming a mean sojourn time of 12 months (n = 31).

Supplementary Table 1. Estimated Median Lead Times in Surveillance Patients (n = 31) for Different Assumptions of the Sojourn Time

Sojourn time	Median lead-time (IQR)	
Months	Months	Days
3	3.0 (0.0)	91.3 (0.5)
6	5.9 (0.4)	179.9 (13.1)
12	10.5 (2.9)	320.4 (87.0)
15	12.2 (4.3)	371.3 (131.5)

The estimated lead time was calculated for each patient using the following formula (from Duffy et al[15]).

$$E(s) = \frac{1 - e^{\lambda t}}{\lambda}$$

Where $E(s)$ is the estimated lead time; λ is 1/sojourn time; and t is follow-up time after diagnosis until death or end of follow-up.

Supplementary Table 2. Survival Outcomes in Non-surveillance (n = 155) and Surveillance (n = 31) Patients, Subdivided by Stage I and Stages II–IV

	Non-surveillance (n = 152)[a]		Surveillance (n = 31)			
Survival outcomes			Unadjusted for lead time		Adjusted for lead time: κ = 12 months	
	Stage I (n = 9)	**Stages III–V (n = 143)**	**Stage I (n = 12)**	**Stages II–IV (n = 19)**	**Stage I (n = 12)**	**Stages II–IV (n = 19)**
Median OS (95% CI), m	NA	4.6 (3.7 – 6.4)	NA	21.7 (16.9 – 35.8)	NA	10.0 (9.1 – 11.4)
Survival rate (95% CI)						
1-year	66.7% (42.0%–100.0%)	23.8% (17.7%–31.9%)	91.7% (77.3%–100.0%)	78.9% (62.6%–99.6%)	73.3% (51.5%–100.0%)	52.6% (34.4%–80.1%)
3-year	NA	6.6% (3.2%–13.8%)	62.9% (39.5%–100.0%)	15.8% (5.6%–44.6%)	62.9% (39.5%–100.0%)	15.8% (5.6%–44.6%)
5-year	NA	3.3% (0.7%–15.9%)	62.9% (39.5%–100.0%)	15.8% (5.6%–44.6%)	62.9% (39.5%–100.0%)	15.8% (39.5%–44.6%)

NOTE. Survival outcomes of patients diagnosed under surveillance are shown unadjusted and adjusted for lead time with an assumed mean sojourn time of 12 months.
NA, not available (median OS or survival rate was not reached); k, mean sojourn time.
aExcluding n ¼ 3 patients with unknown stage.

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