Surveillance for familial and hereditary pancreatic ductal adenocarcinoma

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Colophon

Cover design: Ron Zijlmans

Lay-out: ProefschriftMaken | www.proefschriftmaken.nl

Printing: Global Academic Press

ISBN: 978-94-6469-325-6

The work presented in this thesis was conducted at the department of Gastroenterology and Hepatology, Leiden University Medical Center, The Netherlands and the Foundation for the Detection of Hereditary Tumours.

Financial support for printing this thesis was kindly provided by Leiden University, ChipSoft and ABN AMRO.

Surveillance for familial and hereditary pancreatic ductal adenocarcinoma

Surveillance voor familiair en overerfelijk ductaal adenocarcinoom van de pancreas

Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op donderdag 1 juni 2023

klokke 11.15 uur

door

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geboren te Utrecht

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CHAPTER 1

Introduction

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the most lethal forms of cancer, with a 5-year survival rate of less than 10%. Over the years, the incidence of PDAC in the US increased from 11.42 per 100.000 people in 2017 to 12.91 per 100.000 people in 2020 (1, 2). The risk in men is higher compared to women, 14.70 versus 11.31 per 100.000, respectively (2).
Three percent of all new cancer cases are associated with PDAC, which makes it the 12th on the list of most common cancers in the general US population. The median age at diagnosis is 70 years, with 30% of all cases being diagnosed between the age of 65 and 74 years (2). Currently, PDAC is the third leading cause of cancer death, with a yearly mortality almost as high as the incidence (1, 3). The high mortality is explained by the fact that PDAC becomes symptomatic at a late stage, and only 15% of the tumors are resectable at diagnosis. The only way to improve prognosis is through early detection by screening. However, the risk of PDAC in the general population is too low to justify screening but surveillance of high risk groups might be more attractive.

Familial and hereditary PDAC

In 5% of all cases of pancreatic cancer, hereditary factors play a role in its development (4). These cases are subdivided into two groups: (1) familial and (2) hereditary PDAC. Familial PDAC is the largest group and is usually defined by the presence of at least two first-degree relatives with this cancer in a family (5). The risk of PDAC depends of the number of relatives with the tumor and varies from 8% for individuals with two relatives with PDAC to 30% for those with three relatives with this cancer (4). Hereditary PDAC, 5-10% of all PDAC cases, is defined by the presence of an underlying gene defect. Such gene defects can be identified in 3-5% of (apparently) sporadic PDAC and 3-10% of familial PDAC(6). Table 1 provides an overview of the most frequent underlying gene defects that predispose to PDAC including clinical features and estimated cancer risks (4). The highest risk is observed in individuals with a pathogenic variant in the SSTK-gene (Peutz-Jeghers syndrome) and in the p16 gene (Familial melanoma). Surveillance for PDAC is currently recommended by the International Cancer of the Pancreas Screening (CAPS) consortium if the risk exceeds 5% (5).

Table 1. Gene defects PDAC with clinical features

Gene defect	Risk PDAC until 70 years	Clinical features
CDKN2A (FAMMM)	15-20%	Atypical naevi, malignant melanomas
STK11 (Peutz-Jeghers syndrome)	>20%	Mucocutaneous pigmentation, hamartomatous polyps
BRCA1/2 (HBOC)	3-8%	Breast-, ovarian-, prostate cancer
TP53 (Li-Fraumeni syndrome)	<5%	Sarcoma, breast, leukemia, adrenal gland cancer
PRSS1 (Hereditary Pancreatitis)	40%	Acute recurrent or chronic pancreatitis
Familial Pancreatic Cancer (FPC)	2 First Degree Relatives: 8-12% >3 First Degree Relatives: 16-38%	NA
Lynch Syndrome	<5%	Colorectal, endometrial, urinary tract, stomach, small bowel cancer

Abbreviations: FAMMM: Familial Atypical Multiple Mole Melanoma; HBOC: Hereditary Breast- and Ovarian cancer ; PDAC, pancreatic ductal adenocarcinoma.

Surveillance for Pancreatic Ductal Adenocarcinoma (PDAC)

One of the requirements that should be met before implementing a surveillance program is thorough knowledge of the natural history of PDAC. Several studies have suggested that PDAC originates from precursor lesions including intraductal papillary mucinous neoplasms (IPMN) and pancreatic intraepithelial neoplasia (PanIN) lesions (7-10). IPMNs are epithelial pancreatic cystic tumors of mucin-producing cells that arise from the pancreatic ducts. If an IPMN originates from the main duct, it is referred to as main branch IPMN and if the lesion arises from side branches it is called side-branch IPMN.

PanIN lesions are composed of columnar to cuboidal cells with varying amounts of mucin and varying degrees of cytological and architectural atypia. They are classified into three grades: PanIN-IA (flat) and PanIN-IB (papillary) are low grade lesions with minimal cytological and architectural atypia. PanIN-2 lesions show mild to moderate cytological and architectural atypia. High grade PanINs (PanIN-3) are characterized by severe cytological and architectural atypia.

Both IPMN as well as PanIN-lesions may progress into cancer. The histological progression is paralleled by the accumulation of genetic changes. The early detection and treatment of these precursor lesions may prevent the development of PDAC.

Theresa Brentnall, gastroenterologist in Seattle, US, was the first who reported in 1999 the outcome of surveillance of fourteen individuals from three kindreds with familial PDAC(11). Surveillance using EUS, CT-scanning, ERCP and tumormarkers suggested the presence of dysplasia in seven patients who subsequently underwent total pancreatectomy. All patients had histological evidence of dysplasia in the surgical specimens. The authors concluded that thorough screening of individuals with a family history of PDAC is feasible and that clinical data and imaging studies including EUS and ERCP can be used to identify individuals with dysplasia. Since then, many surveillance studies have been published(12-19).

Hereditary and Familial Melanoma

Familial melanoma is usually defined by the presence of 2 or 3 close relatives with invasive melanoma with or without multipele melanoma in a kindred. In the 1980s, a large number of such families, previously referred to as families with Familial Atypical Multiple Mole Melanoma (FAMMM), were identified in the region of Leiden, The Netherlands, by Professor Wilma Bergman, dermatologist at the Leiden University Medical Centre. Subsequent genetic research by Nelleke Gruis et al. led to the identification of a founder mutation (the Leiden-p16-gene mutation) in the CDKN2A-gene which was responsible for the high frequency of these families with FAMMM in the region (20). All these families were offered surveillance of the skin for the early detection of melanoma (21, 22). By thorough research of a large series of families, Bergman et al. discovered a high frequency of PDAC in FAMMM families. In collaboration with Henry Lynch and Patrice Watson et al., she identified 18 cases of PDAC in twelve families with FAMMM (22). In 1999, we calculated that the life time risk of developing PDAC in P16-Leiden associated families was 15-20% by the age of 70 years which was later confirmed by Snoo & Bishop et al. (23, 24). These high risks and the above-mentioned succesfull study by Brentnall et al. inspired us to start in 2000 a surveillance program for PDAC in families with a confirmed P16-Leiden mutation at the Department of

Gastroenterology & Hepatology of the Leiden University Medical Centre in Leiden, The Netherlands.

Aims of our studies included in this thesis

The aims of our studies were, first, to investigate the outcome of longterm surveillance of P16 carriers and to compare the results of surveillance of P16-families with the surveillance outcome of familial PDAC. (Chapter 2). For this study, we collaborated with the German Familial Pancreatic Carcinoma Registry established by Professor Detlef Bartsch at the University of Marburg in 1999 and the Spanish National Registry in Madrid established in 2009 by Professor Alfredo Carrato. The second aim was to evaluate the natural history and role of precursor lesions including IPMN and PanIN lesions in families associated with a P16-Leiden mutation (Chapter 3). It is common knowledge that hereditary cancer is associated with the development of multiple tumors due to the fact that all body cells carry the inherited mutation. The third aim, therefore, was to evaluate the risk of multiple PDAC in carriers of a P16-Leiden founder mutation (Chapter 4). The fourth aim was to evaluate the cost-effectiveness of surveillance (Chapter 5); this study was performed in collaboration with Dr W. van den Hout, Department of Medical Decision Making at the LUMC.
During our surveillance study, the program unexpectedly detected also other types of cancer than PDAC including benign lesions (incidentaloma). The fifth aim was to evaluate what type of cancers and benign lesions were detected and whether surveillance and early detection offered any benefit (Chapter 6). This study was also performed in collaboration with the German Familial PDAC Registry and the Registry in Madrid.
The final aim was to describe the dilemmas in the management of screen-detected lesions that we experienced during our surveillance program (Chapter 7).

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1

CHAPTER 2

2

The benefit of surveillance for pancreatic cancer in high-risk individuals: Outcome of long-term prospective follow-up studies from three European expert centres

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J. Clin Oncol 2016; 34: 2010-9

Abstract

Purpose

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis. Hereditary factors play a role in the development of PDAC in 3% to 5% of all patients. Surveillance of high-risk groups, may facilitate detection of PDAC at an early stage. The aim of this study was to assess whether surveillance aids detection of early-stage PDAC or precursor lesions (PRLs) and improves the prognosis.

Patients and Methods

Screening outcomes were collected from three European centers that conduct prospective screening in high-risk groups including families with clustering of PDAC (familial pancreatic cancer [FPC]) or families with a gene defect that predisposes to PDAC. The surveillance program consisted of annual magnetic resonance imaging, magnetic resonance cholangiopancreatography, and/or endoscopic ultrasound.

Results

Four hundred eleven asymptomatic individuals participated in the surveillance programs, including 178 CDKN2A mutation carriers, 214 individuals with FPC, and 19 BRCA1/2 or PALB2 mutation carriers. PDAC was detected in 13 (7.3%) of 178 CDKN2A mutation carriers. The resection rate was 75%, and the 5-year survival rate was 24%. Two CDKN2A mutation carriers (1%) underwent surgical resection for low-risk PRL. Two individuals (0.9%) in the FPC cohort had a pancreatic tumor, including one advanced PDAC and one early grade 2 neuroendocrine tumor. Thirteen individuals with FPC (6.1%) underwent surgical resection for a suspected PRL, but only four (1.9%) had high-risk lesions (ie, high-grade intraductal papillary mucinous neoplasms or grade 3 pancreatic intraepithelial neoplasms). One BRCA2 mutation carrier was found to have PDAC, and another BRCA2 mutation carrier and a PALB2 mutation carrier underwent surgery and were found to have low-risk PRL. No serious complications occurred as consequence of the program.

Conclusion

Surveillance of CDNK2A mutation carriers is relatively successful, detecting most PDACs at a resectable stage. The benefit of surveillance in families with FPC is less evident.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with a 5-year survival rate of only 5%.[1] Despite progress in our understanding of PDAC development and improvements in surgical techniques, the survival rate has not substantially changed since the introduction of pancreaticoduodenectomy 80 years ago. Currently, surgical resection is the only potential curative treatment for PDAC, but in approximately 80% of symptomatic patients, the tumor is already unresectable at the time of diagnosis. Improvement in the resectability of tumours requires detection of PDAC at an earlier stage. Selective screening of individuals at high risk for PDAC might be one way to reach this goal. Hereditary factors play a role in the development of PDAC in 3% to 5% of all patients[2], and individuals at increased risk of developing PDAC can be subdivided into those with an underlying gene defect such as *CDKN2A*, *BRCA1/2, PALB2*, and *STK11* mutations and those individuals with a significant family history of PDAC (familial pancreatic cancer [FPC]).[3] The risk of PDAC varies from 5% to 36% depending on the underlying gene defect.[4-7] Disease risk in FPC depends on the number of relatives with PDAC and varies from 8% (two relatives) to 30% (three relatives).[3]

Surveillance of these high-risk groups may lead to early detection of PDAC or detection of precursor lesions (PRLs), allowing curative surgical treatment. However, before undertaking surveillance on a global scale, we need to first establish whether the surveillance program meets the screening criteria set out by Wilson and Jungner.[8] Surveillance of individuals at high risk for PDAC complies with most of these requirements. The target group (ie, individuals with a substantial risk of PDAC [≥ 10%]) is well defined. Although the natural history of the disease is not completely known, studies have reported that patients with FPC as well as carriers of a *CDKN2A* mutation frequently develop PRLs including pancreatic intraepithelial neoplasms (PanINs) and intraductal papillary mucinous neoplasms (IPMNs).[9] Surveillance tools (magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography [MRCP], and endoscopic ultrasound [EUS]) that are able to detect small PRLs are available.[10-14] The surveillance program does not seem to be burdensome for the patients.[15]

However, it is not yet known whether the surveillance program meets the most important criteria, which are the early detection of cancer or PRLs and an improved prognosis. Previous studies reported data on the yields of surveillance but did not address the benefit of programs in terms of survival.[10-14,16-21] In the current study, we evaluated the long-term outcome of prospective surveillance of a large series of *CDKN2A*/*p16-Leiden* mutation carriers, *BRCA1/2* and *PALB2* mutation carriers, and individuals at risk (IARs) for FPC conducted at three expert centers in Marburg, Germany; Leiden, the Netherlands; and Madrid, Spain. The aim of the study was to assess whether surveillance leads to detection of early-stage PDAC or to the detection of relevant PRLs and to evaluate whether the program leads to improvements in prognosis.

Patient and methods

Study Design

The current study was made possible through the collaboration of three tertiary referral centers: the Department of Surgery at Philipps University in Marburg, the Department of Medical Oncology at Ramon y Cajal University Hospital in Madrid, and the Department of Gastroenterology at Leiden University Medical Center in Leiden. The study design was a retrospective evaluation of an ongoing prospective follow-up study. The three centers have conducted screening programs for IARs for PDAC over the past 4 to 15 years. The number of high-risk individuals and the type of hereditary PDAC or type of familial PDAC (ie, families with two first-degree relatives with PDAC [FPC2] or families with at least three first-degree relatives with PDAC [FPC3]) in the three centers are listed in Table 1. Only asymptomatic individuals were offered surveillance.

A detailed description of patient selection has been published previously.[22,23] At Leiden University Medical Center, individuals with the Dutch founder mutation, a 19-base pair deletion of exon 2 of the *CDKN2A* gene *p16-Leiden*, were referred to the Department of Gastroenterology by a clinical geneticist. Only patients with a proven *CDKN2A* mutation or individuals diagnosed with a personal history of melanoma and a known mutation in the family were selected for the program. At Philipps University, a national registry for families with familial PDAC (the FaPaCa Registry) was established in 1999.[24] Individuals from families with two or three first-degree relatives with PDAC were offered surveillance. Members of FPC families were also recruited through physician referral, the counseling office of the Deutsche Krebshilfe, or the FaPaCa Web site. In Madrid, patients were selected through a case-control study of patients with newly diagnosed pancreatic cancer and through 17 familial cancer units set up in Spain.[25] In Leiden, surveillance started at the age of 45 years. In Marburg and Madrid, surveillance started at age 40 or 10 years earlier than the youngest age at diagnosis in the family.

The current study is an update of the outcome of surveillance that was published previously.[22,23] All participants were fully informed of the advantages and disadvantages of the program. The study was approved by the ethics committees of the respective centers.

Surveillance Protocol

The *CDKN2A/p16-Leiden* mutation carriers in Leiden were invited for an annual MRI/MRCP. Beginning in 2012, EUS was also offered as an option in addition to annual MRI. In the event of a small lesion, MRI was repeated 3 to 6 months later. In cases where there was serious suspicion of PDAC, additional EUS and CT scanning was performed. The surveillance program in Marburg included annual screening by MRI with MRCP and EUS between 2002 and 2010. Since 2011, follow-up imaging consisted of annual MRI with MRCP and EUS every third year or in case of suspicious MRI findings. If there was suspicion for a significant abnormality, IARs underwent repeated imaging after 4 weeks supplemented with EUS-guided fine-needle aspiration (FNA) in some individuals. The surveillance program in Madrid included annual EUS and MRI. All patients with

confirmed suspicious lesions at the three centers were discussed within a multidisciplinary team, and a decision was made regarding the need of surgery. The criteria that were generally used to propose surgery were as follows: multiple cystic lesions greater than 10 mm, in particular, cystic lesions that showed significant growth or a solid component; solitary cystic lesions greater than 30 mm; solid lesions greater than 5 mm confirmed by MRI, EUS, and CT-scanning, especially, those that increase in size; a dilated main pancreatic duct (. 10 mm); and positive results of a biopsy.

The surveillance protocols used at the three centers are listed in Table 1. The data collected include number of IARs with a PRL or PDAC, age at diagnosis and surgery, site of the PRL and cancer, type of surgery, complications, histologic type of PRL, stage of PDAC, and survival rate of patients with PDAC. The observation time was from the start of the screening programs until January 1, 2015. In the evaluation of the surveillance program, we consider the program a success if a high-risk PRL (PanIN grade 3 lesions or IPMN with high-grade dysplasia) was detected and treated or an early PDAC (T1N0M0 with negative resection margins) was resected.

Statistical Analysis

Age-specific cumulative incidence of PDAC in the *CDKN2A/p16-Leiden* mutation carriers and the PDAC survival were calculated using Kaplan-Meier survival analysis. Analysis of the data was conducted using the SPSS version 23.0 (SPSS, Chicago, IL).

Table 1. Distribution of Individuals at High Risk for PDAC Under Surveillance at the Three Expert Centers, City and Country of Center

Factor	Marburg, Germany	Leiden, the Netherlands	Madrid, Spain
Year surveillance program began	2002	2000	2010
Current surveillance recommendation	From 2002-2011 annual MRI, MRCP, and EUS; from 2011 to present annual MRI and MRCP, EUS every 3 years or in case of suspicious MRI	Annual MRI; since 2012 option for EUS	Annual MRI and EUS
No. of high-risk individuals per group at January 1, 2015			
FPC2 FPC3	114	—	20
CDKN2A/p16-Leiden	70	—	10
BRCA2/PALB2	—	178	—
	12	2	5
Sex, No. of individuals Male			
Female	81	72	24
	115	106	11
Total No. of MRI surveillance examinations at January 1, 2015	622	866	45
Total No. of surveillance EUSs at January 1, 2015	363	106	72
Average age at start of surveillance, years (range)	45.5 (25-73)	56 (37-75)	46.6 (29-81)
Average follow-up time, years (range)	3.4 (0.0-10.8)	4.4 (0.0-14.1)	1.3 (0.0-3.3)

Abbreviations: EUS, endoscopic ultrasound; FPC2, families with two first-degree relatives with familial pancreatic cancer; FPC3, families with at least three first-degree relatives with familial pancreatic cancer; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma.

Results

CDKN2A/p16-Leiden *Mutation Carriers*

Patient characteristics. One hundred seventy-eight *CDKN2A* mutation carriers comprising 177 *p16-Leiden* mutation carriers and one carrier of a *CDKN2A* (c.67G>C, G23R) mutation were included in the study; 106 of these patients (59.6%) were women, and 72 (40.4%) were men. The mean age at the start of the program was 56 years (range, 37 to 75 years), and the mean follow-up time was 53 months (range, 0 to 169 months). Seventeen patients (9.6%) were lost to follow-up. A total of 866 MRIs and 106 EUSs were performed.

Surveillance outcomes: Pancreatic cancer. PDAC was detected in 13 (7.3%) of the 178 mutation carriers, including eight women and five men. The mean age at diagnosis was 58 years (range, 39 to 74 years). The cumulative incidence of PDAC was 14% by the age of 70 years (Fig 1). Five tumors were diagnosed at first screening, and eight were detected during follow-up. Four tumors were located in the head of the pancreas, five in the tail, three in the body, and one in the transition area from head to body (Table 2). Nine patients underwent surgery, including three who underwent a distal pancreatectomy, two a Whipple procedure, one a subtotal pancreatectomy, one a resection of the body and a distal pancreatectomy, and two a distal pancreatectomy including splenectomy. In five (56%) of the nine patients, the lymph nodes were free of tumor, and in seven (78%) of nine patients, the resection margin was free of tumor. Of the four patients who did not undergo surgery, two patients had distant metastasis of PDAC, and a third patient had extensive local disease. The fourth patient was found to have a small resectable pancreatic lesion but did not undergo surgical resection as a result of extensive pulmonary metastasis of a melanoma. The MRI images suggested that the pancreatic mass was a PDAC and not a melanoma metastasis. The overall resection rate was 75%. One patient developed a second PDAC 54 months after a Whipple procedure of the primary tumor and underwent a distal pancreatectomy.[26] Eight of the 13 patients died; seven patients died as a result of PDAC, and one patient died as a result of melanoma metastases. The overall 5-year survival rate was 24% (Fig 2). In terms of screening efficiency, 14 patients needed to be screened to detect one PDAC, and a total of 67 MRIs were needed to detect one PDAC.

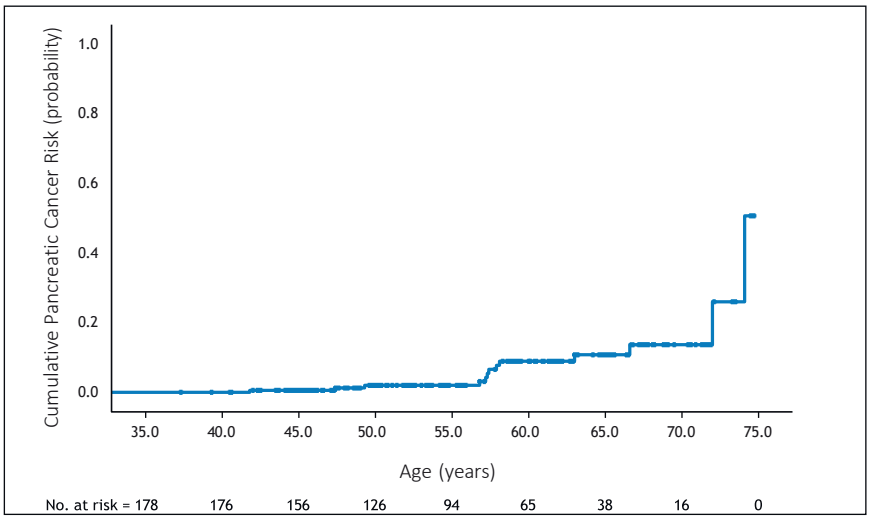

Fig 1. Cumulative incidence of pancreatic ductal adenocarcinoma for *CDKN2A/p16* mutation carriers.

Surveillance outcomes: PRLs. In 26 (14.6%) of 178 *CDKN2A/ p16-Leiden* mutation carriers, a cystic lesion was found. Two individuals (1%), both women, underwent surgery (Table 2). In the first patient, the initial MRI/MRCP (2001) at the age of 63 years showed multiple ductectasia in side branches in the body of the pancreas with a diameter of 15 mm. In 2008, there was slight growth of the lesion, and an extended distal pancreatectomy was subsequently performed. Histologic examination revealed multi-focal PanIN grade 1 to 2 lesions with branch duct (BD) IPMN and severe multifocal lobulocentric fibrosis. The patient is currently doing well 7.2 years later.
The second patient underwent a Whipple procedure at the age of 67 years as a result of a 15-mm solid lesion in the uncinate process detected at first MRI. Histologic examination revealed an IPMN gastric type with low-grade dysplasia. Seventeen months after surgery, the patient has slightly increased serum values of alkaline phosphatase and g-glutamyltransferase but is asymptomatic and in a good health.

IARs for FPC

Patient characteristics. This patient group included 214 individuals, including 99 men and 115 women. One hundred thirty-four individuals were from FPC2 families, and 80 were from FPC3 families. Average age at start of the surveillance program was 48.2 years (range, 27 to 81 years), and the mean follow-up time was 2.8 years (range, 0.0 to 10.8 years). A total of 618 MRIs and 402 EUSs were performed as part of the follow-up program.

Table 2. Detailed Information on *CDKN2A* Mutation Carriers Who Underwent Pancreatic Resection Under Surveillance Interval From

Patient No.	Age (years)/Sex	MRI Findings	MRI to Cancer Diagnosis (months)	Findings at Previous MRI	Management Histology	Staging	TNM	Outcome	Cause of Death
1	72/F	22-mm tumor in head-body	11.3	Two duct ectasias	Subtotal pancreatectomy (excluding duodenum)	Well-differentiated ductal adenocarcinoma, resection margin positive; one of two nodes positive	T4N1M0	Died 4.5 months after diagnosis	PDAC
2	57/F	CT scan: 48-mm tumor in tail	4	In retrospect, there was a 1-cm lesion visible	No surgery because of liver metastases	—	T3NxM1	Died 15 months after diagnosis	PDAC metastases
3	58/M	10-mm tumor in body	5.1	Slightly irregular pancreatic duct	No surgery because of pulmonary metastases of melanoma	—	T1N0M0	Died 10 months after diagnosis	Melanoma metastases
4	58/M	30-mm tumor in tail	12.2	Normal	Distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin positive; four of four nodes positive	T4N1M0	Died 22 months after diagnosis	PDAC
5	63/F	20-mm tumor in head	12.0	Normal	Unresectable	Adenocarcinoma distant metastases with positive nodes in transverse mesocolon	T2N3M1	Died 8 months after diagnosis	PDAC metastases
6	56/F	9-mm tumor in tail	12.3	Normal	Distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 10 nodes positive	T1N0M0	Alive 25 months after diagnosis	—
7	57/F	36-mm tumor in tail	28.3	Normal	Distal pancreatectomy including splenectomy	Ductal adenocarcinoma, resection margin free	T2N0M0	Died 21 months after diagnosis	PDAC metastases
8	58/M	CT scan: 35-mm tumor in head	9.6	Normal	Unresectable	—	T4NxM0	Alive 6 months after diagnosis	—
9	62/F	5-mm tumor in head-body 7-mm tumor in corpus-tail	Not applicable	—	Whipple Distal pancreatectomy including splenectomy	Well-differentiated ductal adenocarcinoma, resection margin free; zero of seven nodes positive Well-differentiated ductal adenocarcinoma, resection margin free; zero of 13 nodes positive	T1N0M0 T1N0M0	Alive 73 months after diagnosis	—
10	49/M	37-mm tumor in tail	Not applicable	—	Distal pancreatectomy including splenectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; zero of 15 nodes positive	T3N0M0	Died 35 months after diagnosis	PDAC metastases
11	74/F	15-mm tumor in tail	12.2	Stenosis pancreatic duct	Distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; zero of five nodes positive	T1N0M0	Alive 6 months after diagnosis	—
12	47/F	57-mm tumor in body	Not applicable	—	Resection of pancreatic body and distal pancreatectomy	Moderately differentiated ductal adenocarcinoma, resection margin free; four of 15 nodes positive	T3N1M0	Died 18 months after diagnosis	PDAC

(Continued on following page)

Table 2. Detailed information on *CDKN2A* Mutation Carriers Who Underwent Pancreatic Resection Under Surveillance (continued)

Patient No.	Age (years)/ Sex	MRI Findings	Interval From Previous MRI to Cancer Diagnosis (months)	Findings at Previous MRI	Management	Histology	TNM Staging	Outcome	Cause of Death
13	39/M	23-mm tumor in head	Not applicable	—	Whipple	Moderately differentiated ductal adenocarcinoma, resection margin free; four of 24 nodes Positive	T2N1M0	Alive 36 months after diagnosis	—
14	63/F	17-mm cystic lesion in body	3.9	15-mm cystic lesion in body	Distal pancreatectomy	Multifocal PanIN grade 1-2, BD-IPMN and severe multifocal fibrosis	—	Alive 87 months after diagnosis	—
15	67/F	15-mm solid lesion in head	Not applicable	—	Whipple	IPMN gastric-type LGD	—	Alive 17 months after diagnosis	—

NOTE. Patients 1, 3 to 8, 11, and 14 had an incident pancreatic ductal adenocarcinoma (PDAC) or precursor lesions (PRLs); patients 2, 9, 10, 12, 13, and 15 had a prevalent PDAC or PRLs. Patient 2 underwent CT scanning because of abdominal symptoms 4 months after a normal MRI scan and was found to have an unresectable tumor. In retrospect, a 10-mm lesion was found. Patient 8 presented with jaundice 9.6 months after a normal MRI scan. He was found to have an unresectable tumor in the head of the pancreas. Patient 5 developed abdominal symptoms 12 months after a normal MRI and was found to have a 20-mm solid lesion in the head of the pancreas with distant metastases.

Abbreviations: BD, branch duct; CT, computed tomography; F, female; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; M, male; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasm

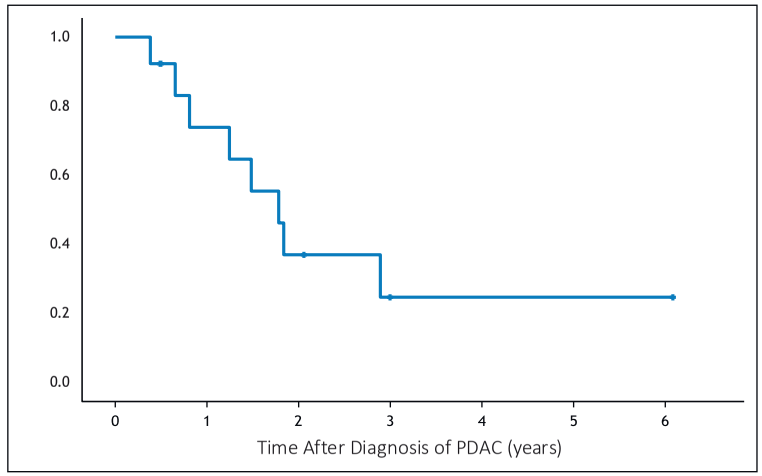

Fig 2. Overall survival of *CDKN2A*/*p16* mutation carriers with pancreatic ductal adenocarcinoma (PDAC) detected during surveillance.

Table 3. Detailed Information on Individuals at Risk for FPC Who Underwent Pancreatic Resection

Patient No.*	Age(years)/Sex	Disorder	MRI Findings	Incident or Prevalent	Management	Histology	Outcome	Cause of Death
1	52/M	FPC2	Dilated main pancreatic duct with stenosis, head	Prevalent	Whipple	Main duct IPMN HGD	Alive 30 months after surgery	—
2	58/F	FPC2	Multiple (2-8 mm) cystic lesions, body and tail	Incident	Total pancreatectomy	Multifocal PanIN grade 2, BD-IPMN LGD, AFL	Died 22 months after surgery	Klatskin tumor
3	52/F	FPC3	Two ductectesia (5 and 7 mm)	Incident	Total pancreatectomy	Multifocal PanIN grade 2, PanIN grade 3, AFL	Alive 55 months after surgery	—
4	64/F	FPC2	Multiple (2-13 mm) cystic lesions, body and tail	Incident	Total pancreatectomy	Multifocal PanIN grade 2, PanIN grade 3, BD-IPMN LGD, AFL	Alive 49 months after surgery	—
5	69/F	FPC3	Multiple (3-10 mm) ductectesia, body and tail	Prevalent	Total pancreatectomy	Multifocal PanIN grade 2, PanIN grade 3	Alive 16 months after surgery	—
6	47/M	FPC3	10-mm cystic lesion, head	Incident	Whipple	Multifocal PanIN grade 2, BD-IPMN LGD	Alive 29 months after surgery	—
7	54/F	FPC3	Multiple cystic lesions (3-10 mm), body and tail	Incident	Distal pancreatectomy	Multifocal PanIN grade 2, BD-IPMN LGD, AFL	Alive 3 months after surgery	—
8	53/F	FPC3	8-mm hypointense lesion, tail	Incident	Distal pancreatectomy	PanIN grade 2, BD-IPMN LGD	Alive 88 months after surgery	—
9	55/M	FPC3	6-mm hypointensive lesion, tail	Prevalent	Distal pancreatectomy	Lobular fibrosis with PanIN grade 1 lesion	Alive 94 months after surgery	—
10	60/M	FPC2	7-mm hypointense lesion, tail	Prevalent	Distal pancreatectomy	Focal fibrosis with PanIN grade 1 lesion	Alive 120 months after surgery	—
11	61/F	FPC3	Cystic lesions (14 and 22 mm), head and tail	Prevalent	Distal pancreatectomy	Serous cystadenoma	Alive 132 months after surgery	—
12	42/F	FPC2	Lobulated 32-mm macrocystic lesion, tail	Incident	Distal pancreatectomy	Serous cystadenoma	Alive 98 months after surgery	—
13	61/F	FPC2	Normal (EUS 6-mm hypoechogenic lesion, body)	Incident	Distal pancreatectomy	Serous cystadenoma	Alive 86 months after surgery	—
14	53/F	FPC3	24-mm solid lesion, head; small cystic lesions, body and tail	Incident	Total pancreatectomy	Ductal adenocarcinoma; 9 of 22 nodes positive, pT3N1M0	Died 38 months after surgery	PDAC metastases

Table 3. Detailed Information on Individuals at Risk for FPC Who Underwent Pancreatic Resection (continued)

15	47/F	FPC3	10-mm cystic lesion	Prevalent	Distal pancreatectomy including splenectomy	FNA biopsy: malignant cells; surgical specimen: serous cystadenoma, no (residual) cancer	Alive 13 months after surgery	—
16	48/F	FPC2	Normal (EUS 5-mm solid lesion in body)	Prevalent	Distal Pancreatectomy	T1 grade 2 neuroendocrine tumor, resection margins free; no positive nodes	Alive 28 months after surgery	—

Abbreviations: AFL, atypical flat lesion; BD, branch duct; EUS, endoscopic ultrasound; F, female; FNA, fine-needle aspiration; FPC, familial pancreatic cancer; FPC2, families with two first-degree relatives with familial pancreatic cancer; FPC3, families with at least three first-degree relatives with familial pancreatic cancer; HGD, high- grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; M, male; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasm; PDAC, pancreatic ductal adenocarcinoma.

*Patient 15 underwent surgery in Madrid, Spain; all other patients underwent surgery in Marburg, Germany.

Table 4. Detailed Information on *BRCA2* and *PALB2* Mutation Carriers Who Underwent Pancreatic Resection

Patient No. (years)	Age/ Sex	Disorder	MRI Findings Outcome	Incident or Prevalent	Management	Histology	Alive/death	Cause of Death
1	68/F	*BRCA2*	Solid lesion (17 3 12 mm) in the tail	Incident	Distal pancreatectomy	Ductal adenocarcinoma; resection margins free; zero of 16 lymph nodes positive	Died 17 months after surgery	PDAC metastases
2	71/F	*PALB2*	Multiple cystic lesions (3-7 mm) in head	Prevalent	Whipple	Multifocal PanIN grade 2, BD-IPMN LGD	Alive 21 months after surgery	—
3	67/F	*BRCA2*	Multiple cystic lesions (3-8 mm) in body and tail	Prevalent	Total pancreatectomy	Multifocal PanIN grade 2, AFL	Alive 10 months after surgery	—

Abbreviations: AFL, atypical flat lesion; BD, branch duct; F, female; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasm; PDAC, pancreatic ductal adenocarcinoma.

*All patients underwent surgery in Marburg, Germany.

Surveillance outcomes: Pancreatic cancer. In the FPC group, the program detected a lesion suspected for PDAC in three female patients (1.4%). The first patient was a 53-year-old member of an FPC3 family. She missed two MRI screening visits and was diagnosed 26 months after the last normal screening visit with a 30-mm solid tumor in the head of the pancreas. The patient underwent a total pancreatectomy. Histologic examination showed a ductal adenocarcinoma pT3N1 (nine positive lymph nodes out of 22) M0 with tumor-free resection margins. The patient died 38 months after surgery as a result of metastatic disease.

The second patient was a 47-year-old member of an FPC3 family. At the first EUS, a 7-mm cystic lesion was visible in the body of the pancreas, which was subsequently confirmed by

CT scanning. Two years later, the lesion was 10 mm. An EUS-guided FNA biopsy revealed malignant cells. The patient subsequently underwent a distal pancreatectomy and splenectomy. The surgical specimen showed a serous cystadenoma with atypical changes but no cancer. This patient is alive 1 year after surgery.
The third individual was a member of an FPC2 family. EUS at the age of 48 revealed a 5-mm solid lesion in the tail of the pancreas. FNA biopsy showed a grade 2 neuroendocrine tumor. After distal pancreatectomy, the surgical specimen showed a T1 grade 2 neuroendocrine tumor, with tumor-free lymph nodes and resection margins. The patient is alive 2 years after surgery. *Surveillance outcomes: PRLs.* Cystic lesions were detected in 112 (52%) of 214 IARs. A total of 13 patients (6.1%) underwent surgical resection because of suspicious lesions. The average age at surgery was 56 years (range, 42 to 69 years). Six IARs belonged to FPC2 families, and seven IARs belonged to FPC3 families.
Suspicious lesions were diagnosed at the first examination in five IARs (38.5%) and during follow-up in eight IARs (61.5%). The lesions were mainly located in the pancreatic body and tail of IARs (n = 11); two IARs had suspicious lesions in the pancreatic head (Table 3).
Seven patients underwent a distal pancreatectomy, five patients a total pancreatectomy, and one patient a Whipple procedure. One additional patient underwent surgical exploration because of a suspicious lesion, but no abnormalities were found.
High-risk PRLs, including grade 3 PanIN (n = 3) and IPMN gastric type with high-grade dysplasia (n = 1), were detected on histopathologic analysis in four (1.9% of all screened cases) of 13 IARs. Another four IARs revealed multifocal grade 2 PanIN lesions in combination with BD-IPMNs of the gastric type and/or atypical flat lesions,[27] whereas three IARs showed serous cystadenomas and two IARs showed focal fibrosis with grade 1B PanIN lesions. Thus, five IARs (2.3%) were overtreated.
Four of 13 IARs developed postoperative complications, including three who developed a pancreatic fistula and one who had had a postoperative bleeding after Whipple resection at the pancreaticogastrostomy, which could be managed endoscopically. Twelve IARs are alive without evidence of relevant pancreatic lesions after a median follow-up of 52 months. One female patient developed an adenocarcinoma of the biliary tract 22 months after surgery and died as a result of liver failure.

BRCA1/2 *or* PALB2 *Mutation Carriers*

Patient characteristics. Nineteen individuals carried a *BRCA1/ 2* or *PALB2* mutation, including seven men and 12 women. One individual had a *BRCA1* mutation, 12 individuals had a *BRCA2* mutation, and six individuals had a *PALB2* mutation. Average age at start of the program was 52.6 years (range, 25 to 70 years), and the average follow-up time was 32.7 months (range, 1 to 119 months).
Surveillance outcomes. In this cohort, only one individual (3.8%), a woman with a *BRCA2* mutation, developed PDAC (Table 4). The lesion was detected at age 68 years. The previous MRI 1 year before revealed a small side BD-IPMN at the transition from head to body. The patient underwent a distal pancreatectomy that showed a 19-mm lesion in the tail; resection margins were free, and all lymph nodes were negative (zero of 16 nodes). Seventeen months after surgery, the patient died as a result of liver metastasis.
Two individuals underwent surgery for cystic lesions. The first patient was a 71-year-old

woman with a *PALB2* mutation. She underwent a Whipple procedure after finding a 12-mm lesion on the first MRI and EUS. Histology showed multifocal grade 2 PanIN lesions and BD-IPMNs with low-grade dysplasia. The patient is in good condition 21 months after surgery. The second patient was a 67-year-old woman with a *BRCA2* mutation. Multiple cystic lesions (3 to 8 mm) were detected on the first MRI. She demanded to undergo a total pancreatectomy. Histology showed multifocal grade 2 PanIN and atypical flat lesions. The patient is in good health 10 months after surgery.

Discussion

The current study demonstrated that the resection rate of screen-detected PDAC in *CDKN2A/p16-Leiden* mutation carriers (75%) was much higher than reported for sporadic PDAC patients (15% to 20%) and for historical controls of *CDKN2A/p16-Leiden* mutation carriers with symptomatic PDAC (15%).[23] The 5-year survival rate was substantially higher (24%) than the survival rate reported for patients with symptomatic sporadic PDAC (4% to 7%).[28]

PRLs were much more frequent in patients with FPC than in *CDKN2A/p16-Leiden* mutation carriers. Surgical resection was performed in 13 patients (6.1%) with FPC. According to the definition of high-risk lesions proposed by the expert group,[29] only four lesions (1.9% of all screened patients) were high-risk lesions (grade 3 PanIN or high-grade gastric-type IPMN). However, another four IARs showed multifocal grade 2 PanIN lesions in combination with low-grade gastric-type BD-IPMNs and/or atypical flat lesions. Thus, the question arises of whether multi-focal grade 2 PanIN lesions and low-grade IPMNs are also relevant PRLs for PDAC in the setting of FPC. In a large autopsy study, grade 2 PanIN lesions (previously referred to as atypical hyperplasia or low-grade dysplasia) were reported in 29% of patients with PDAC and only 0.7% of individuals without PDAC, suggesting that grade 2 PanIN lesions are also strongly associated with PDAC development.[30] Although the time interval and rate at which grade 2 PanIN lesions progress to invasive cancer is unknown, one can hypothesize that multifocal grade 2 PanIN lesions and atypical flat lesions are biologically relevant in the setting of FPC.[27]

The strengths of the current study were the design as a prospective long-term follow-up study and the inclusion of a large series of high-risk individuals. In addition, family history in patients with FPC was verified by medical and pathology reports in greater than 95% of all patients. Furthermore, all participants in the Leiden series were found to have either a *CDKN2A* mutation or a personal history of melanoma and a close relative with a *CDKN2A* mutation. A weakness of the study was the lack of a control group.

One of the most important criteria defined by Wilson and Jungner[8] was that surveillance should improve prognosis. Without a control group, it is difficult to determine with certainty the effects of the surveillance program on PDAC outcome. However, in view of the high resection rate and the better survival compared with the survival rates reported for patients with sporadic PDAC, surveillance of *CDKN2A/p16-Leiden* carriers complies with this requirement.

However, whether surveillance of FPC families meets this criterion is still questionable. The yield of PDAC is low (0.9%), and most screen-detected PDACs reported in the literature were advanced cancers.[3] Likewise, the yield in terms of detection of relevant PRLs (grade 3

PanIN and high-grade IPMN) was low (1.9%). However, if surgical removal of multi-focal grade 2 PanIN and multifocal BD-IPMNs is regarded as beneficial, the diagnostic yield increases to 3.7% (eight of 214 patients), and surveillance of FPC might also be considered effective.

In summary, surveillance of *CDNK2A* mutation carriers was relatively successful, detecting most PDACs at a resectable stage. The value of surveillance of FPC is still not clear, and the main effect seems to be prevention of PDAC by removal of PRLs.

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CHAPTER 3

High growth rate of pancreatic ductal adenocarcinoma in CDKN2A-p16-Leiden mutation carriers

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Cancer Prevention Research 2018;11:551-556

Abstract

CDKN2A-p16-Leiden mutation carriers have a 20% to 25% risk of developing pancreatic ductal adenocarcinoma (PDAC). Better understanding of the natural course of PDAC might allow the surveillance protocol to be improved. The aims of the study were to evaluate the role of cystic precursor lesions in the development of PDAC and to assess the growth rate. In 2000, a surveillance program was initiated, consisting of annual MRI in carriers of a CDKN2A-p16-Leiden mutation. The study cohort included 204 (42% male) patients. Cystic precursor lesions were found in 52 (25%) of 204 mutation
carriers. Five (9.7%) of 52 mutation carriers with cystic lesions and 8 (7.0%) of 114 mutation carriers without cystic lesions developed PDAC (P . 0.56). Three of 6 patients with a cystic lesion of 10 mm developed PDAC. The median size of all incident PDAC detected between 9 and 12 months since the previous normal MRI was 15 mm, suggesting an annual growth rate of about 15 mm/year. In conclusion, our findings show that patients with and without a cystic lesions have a similar risk of PDAC. However, cystic precursor lesions between 10 and 20 mm increase the risk of PDAC substantially. In view of the large size of the screen-detected tumors, a shorter interval of screening might be recommended for all patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal form of cancer, with a 5-year survival rate of only 5% to 7% (1). Early detection may improve the prognosis of PDAC. Due to the overall low incidence of the disease and the lack of easily applicable screening tools, population-based screening for PDAC is currently not recommended. However, surveillance of individuals with an increased risk of PDAC might be more valuable and has increasingly been implemented worldwide over the last 15 years (2–9). It has been reported that 3% to 10% of patients with PDAC have a positive family history for this cancer (10). An estimated 3% to 5% of all PDAC are caused by an underlying gene defect (11). *CDKN2A* mutations together with *BRCA2*-, *ATM*- and *PALB2* mutations are the most frequent identi*fi*ed gene defects (12). In the Netherlands, a founder mutation in the *CDKN2A* gene, a 19-base pair deletion called *p16-Leiden*, is the most common cause of familial melanoma and PDAC. The lifetime risk of PDAC in *CDKN2A-p16-Leiden* mutation carriers is 20% to 25% (7, 13). In a recent multicenter study, we demonstrated that annual surveillance of a large Dutch cohort of *CDKN2A- p16-Leiden* mutation carriers using MRI resulted in a higher resection rate of screen-detected PDAC compared with symptomatic PDAC (7). Although this study was the *fi*rst to demonstrate success in detecting early cancers in a high-risk population (14), the surveillance program did not prevent all cancer deaths. Thorough understanding of the natural course of PDAC might be helpful to improve the screening protocol.

Pancreatic intraepithelial neoplasms (PanIN) and intraductal papillary mucinous neoplasms (IPMN) have been identi*fi*ed as common precursor lesions of PDAC (15–17). Recently, we reported a lower frequency of cystic precursor lesions in *CDKN2A-p16-Leiden* mutation carriers compared with patients from families with familial pancreatic cancer

(FPC; ref. 18). This observation suggests that the process of carcinogenesis in *CDKN2A-p16-Leiden* mutation carriers might be different from that in FPC. To further understand this issue, we needed to determine whether cystic precursor lesions increase in size over time and develop into PDAC. If cystic lesions indeed play a role in carcinogenesis in this high-risk group, surveillance would be better targeted to patients with cystic precursor lesions. Finally, information on the growth rate of PDAC might be helpful in decision making regarding appropriate screening intervals.
The main aims of the present study are, therefore, (1) to evaluate the role of precursor lesions in the development of PDAC in *CDKN2A-p16-Leiden* mutation carriers and (2) to assess the size of screen-detected PDAC in relation to the screening interval.

Patients and Methods

Prospective surveillance cohort

In 2000, a surveillance program was initiated in *CDKN2A* mutation carriers (*n* ¼ 204), including 201 with a *CDKN2A-p16-Leiden* founder mutation and 3 with a pathogenic *CDKN2A* variant. The median follow-up is 5.0 years (0.2–15.6 years). The program consists of annual MRI and, optionally, endoscopic ultrasound (EUS) at 6 months. In case of a highly suspicious lesion, additional EUS and CT-scanning is performed within 2 to 3 weeks. If there is little suspicion of malignancy, the MRI is repeated within 3 to 6 months. A detailed description of the surveillance protocol has been published previously (7, 8). The study was approved by the Institutional Review Board of the Leiden University Medical Centre (P00.107). Oral or written informed consent was received from all patients.

MRI techniques

MRI examinations were performed on a 1.5-T between 2000 and 2012 and since 2012 a 3T scanner (Philips). The examinations included T2-weighted images, (3D) MRCP series, and dynamic series before and after intravenous administration of contrast (Dotarem).

Data collection

Patients were selected for the study on the basis of a proven *CDKN2A* mutation. We re-evaluated the most recent MRI examination for all study participants. If a cystic lesion was detected, all previous MRI examinations were re-evaluated to assess whether the cystic lesion was already present at any earlier time point. The size of the cyst on all examinations was recorded. In a few cases with cystic lesions, the initial MRI examinations could not be re-evaluated due to insuf*fi*cient resolution. If these cystic lesions were stable over many years but could not be detected on the *fi*rst "old" suboptimal quality MRI examinations, we considered these lesions as "probably prevalent" cystic lesions. Data were collected on the type of lesions (cysts or IPMN), type of IPMN (side branch, main branch, or mixed IPMN), size, location, and multiplicity of the lesions. Side-branch IPMN was suspected if there was communication of the cystic

lesion with the main duct. Main duct IPMN was de*fi*ned as diffuse or segmental dilatation of the main pancreatic duct of >10 mm without any signi*fi*cant lesion except for IPMN (19). Progression of cysts or IPMN was de*fi*ned as an increase in diameter of 2:3 mm or the development of PDAC. All studies were read on a digital PACS-workstation by a single abdominal radiologist (M.N. Wasser) with more than 20 years of MRI-reading experience.

Screen-detected PDAC
The collected data for all screen-detected PDAC included the size at diagnosis and the interval since the previous MRI. The size was based on measurements of the tumor in the surgical specimen or measurements of the diameter of the tumor on imaging. Previous MRI examinations were evaluated to assess whether cystic lesions were visible in retrospect, as well as the increase in diameter of these lesions over time. In addition, we evaluated the relation between the size of the PDAC at diagnosis and the surveillance interval.

Statistical analysis
The observation time was from the *fi*rst until the last MRI performed before January 1, 2017. The Pearson x^2 test and Student *t* test were used to compare variables between groups. The tests were considered statistically signi*fi*cant if $P < 0.05$. Data analysis was carried out in SPSS v. 22 for MAC.

Results

The study cohort included 204 patients (42% male) with a *CDKN2A*-mutation (mean age, 52 years; SD 8.0). A total of 11 patients (5.4%) were lost to follow-up. Of the 204 mutation carriers, 52 (25%) were found to have at least one prevalent cystic lesion including 2 patients with a prevalent PDAC. The total number of prevalent cysts was 98, 71 (72%) of which were suspected side-branch IPMN. Median cyst size was 3 mm (range, 2–19 mm), and 87 (89%) of the 98 cysts were smaller than 10 mm.
A total of 166 of the 204 patients in the study group had at least 2 MRIs. Fifty-two patients (31%) were found to have at least 1 prevalent or incident cystic lesion. The median follow-up of all patients with >2 MRIs from the *fi*rst to the most recent MRI was 5.0 years (range, 0.2–15.6 years). Growth (3 mm or more) of a cystic lesion was observed in 7 (13.4%) of the 52 patients with prevalent or incident cysts. Six of the 52 patients had at least 1 cystic lesion of 10 mm or more, 3 of which developed PDAC. Five of all 52 (9.6%) patients with an incident or prevalent cystic lesion developed a PDAC after a mean follow-up of 6.5 years (SD 4.2). Three of these cancers developed at the site of the cyst (Table 1). Eight (7.0%) of the 114 patients with at least 2 MRIs and without a prevalent or incident cystic lesion developed PDAC (*P* ¼ 0.56) after a median follow-up of 5.4 years (range, 0.5–15.6 years). The characteristics of the patients with and without cystic precursor lesions are shown in Table 2.
A total of 18 PDACs (7 males) were detected by the surveillance program in the 204

mutation carriers. One patient was excluded because the diameter of the tumor could not be determined. The mean age at diagnosis was 57.8 years (SD 8.9). Five (29%) of the cancers were detected at *first* screening and 12 (71%) during follow-up. The median follow-up of the 12 incident PDAC since the previous normal MRI was 12 months (range, 5–28 months). The size of the screen-detected PDAC in relation to the interval since the previous normal MRI is shown in Fig. 1. The median size of all screen-detected incident PDAC was 17 mm (range, 9–39 mm). The median size of the PDACs detected between 9 and 12 months since the last normal MRI was 15 mm (range, 9–39 mm).

Table 1. Characteristics of patients with incident PDAC detected in the patients with cystic lesions

Patient number/sex (M/F)	Age at diagnosis (years)	Interval since previous MRI (months)	Size of cystic lesions at previous MRI	Site and size of PDAC	TNM staging
1. F	72	11	Head 13 mm Body 7, 8 mm Tail 2, 2, 3 mm	Head 22mm	T4N1M0
2. F	67	21	Head 6 mm Uncinate 13 mm Body 19 mm	Head Diameter unknown	TxNxM0 Irresectable tumor
3. F	64	2	Tail 14 mm Head 17 mm[a]	Head/uncinate process 29mm	T2N3M1
4. F	67	11	Tail 8 mm	Head 13mm	T1N1M0
5. F	51	4.5	Head 3,3,3,3 mm Tail 3mm	Body 18mm	T1N0M0

[a]12 months after the normal previous MRI, a new cystic lesion of 17 mm was found; subsequent imaging 2 months later showed a tumor which was retrospectively also present at the previous MRI.

Table 2. Characteristics of patients with and without cystic lesions

	With cystic lesions	Without cystic lesions	P value
Number of patients	52	114	
Sex distribution (M/F; male %)	18/34 (M 35%)	45/69 (M 39%)	0.55
Mean age first MRI (years)	52.6 (SD 7.2)	51.5 (SD 7.8)	0.36
Mean/median follow-up time since first MRI (years)	6.5 (SD 4.2)	5.4 (0.5–15.6)	0.08
Median follow-up time since diagnosis of cystic lesion (years)	4.3 (0.2–13)	n.a.	n.a.
Number of PDAC	5 (9.6%)	8 (7%)	0.56

Abbreviation: n.a., not applicable.

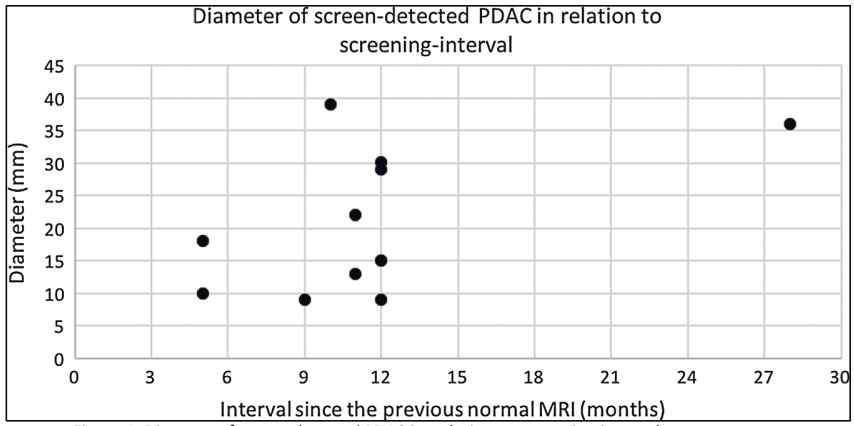

Figure 1. Diameter of screen-detected PDAC in relation to screening interval.

Discussion

To investigate the role of cystic precursor lesions in the development of PDAC in high-risk individuals, we evaluated the outcome of MRI-based surveillance in a large cohort of *CDKN2A-p16-Leiden* mutation carriers. Cystic lesions were found in a quarter of all mutation carriers.

Although most cystic lesions remained stable over time, 3 of 6 patients with at least 1 cystic lesion between 10 and 20 mm developed PDAC. Considering the entire group of mutation carriers, 5 patients with a cystic lesion (9.6%) developed PDAC and a similar proportion (7.0%) developed PDAC in the absence of cysts. The median size of all incident screen-detected PDAC was 17 mm (range, 9–39 mm).

It is generally accepted that PDAC originates from neoplastic epithelial proliferation, including PanIN lesions and IPMNs. The cystic lesions detected by imaging may represent such lesions (7, 18, 20). The prevalence of cystic lesions in our cohort appears to be comparable with frequencies reported in the general population (0.7% to 44.7%; refs. 21–26).

In the present study, 5 (9.6%) of the 52 *CDKN2A-P16- Leiden* mutation carriers with cystic lesions developed PDAC. This is higher than reported in population studies that examined the malignancy rate of cystic lesions (27, 28). However, we also found that the malignancy rate (7.0%) in mutation carriers without a cystic lesion was similar to the rate in the mutation carriers with cystic lesions. Moreover, two out of *fi*ve mutation carriers with cystic lesions developed PDAC at a site other than the site of the cysts. On the other hand, 3 of 6 patients with a cystic lesion between 10 and 20 mm developed PDAC at the site of the cyst.

In order to investigate further possibilities for improvement of the surveillance program, we evaluated the size of screen-detected PDACs in relation to the screening interval. The median size of PDAC detected 9 to 12 months since the previous normal MRI was 15 mm, indicating a growth rate of about 15 mm per year.

What are the explanations for our *fi*ndings? In previous studies, we reported that cystic precursor lesions were less common in carriers of a *CDKN2A*-p16-Leiden mutation compared with individuals with FPC (7, 18). In contrast, the risk of PDAC was much higher in *CDKN2A*-p16-Leiden mutation carriers compared with FPC individuals. These *fi*ndings suggest that cystic precursor lesions play a minor role in the development of PDAC in *CDKN2A*-p16-Leiden mutation carriers. The similar risk of PDAC observed in patients with and without cystic precursor lesions in the current study is in agreement with this hypothesis.

The development from PanIN grade 1 into PanIN grades 2 and 3, and ultimately PDAC is characterized by accumulation of mutations in genes associated with the development of PDAC including alterations of K-RAS, CDKN2A/P16, TP53, and DPC4 genes. Because the patients in our cohort have already such a (germline) mutation at birth, carcinogenesis and development of PDAC may be accelerated. Such accelerated development of PDAC arising from early (invisible) PanIN lesions may explain the similar risk of PDAC observed in the current study in patients with and without cystic precursor lesions. It may also explain the early age of diagnosis of screen-detected PDAC (56 years vs. 66 years reported for sporadic PDAC) and the high growth rate. More studies are needed to con*fi*rm this hypothesis.

The current study has several strengths. Firstly, two particularly robust aspects of the study were the prospective design and the long duration of follow-up. Secondly, the study group is the largest homogeneous group of carriers under surveillance, with almost all carrying a Dutch founder mutation. A limitation of the study is that the quality of the MRI technique changed over time with the replacement of a 1.5 T system by a 3.0 T system in 2012. A second limitation is that as the current study predominantly included individuals with a single Dutch founder mutation in *CDKN2A*, it may not be generalizable to other individuals with hereditary pancreatic cancer.

What are the consequences of our *fi*ndings for clinical practice? In average risk subjects with cystic lesions suspected for BD-IPMNs, resection is considered if the patient has symptoms attributable to the cyst(s), if the cysts are >3 cm in size, or if the cysts contain mural nodules (17). At the meeting of the International Cancer of the Pancreas Screening Consortium (29), there was no consensus on the size criterion for resection of cystic lesions in high-risk individuals, but the majority agreed that surgery should be considered for suspected BD-IPMNs which were 2.2 cm. Although larger studies are needed to con*fi*rm our *fi*ndings, a more aggressive approach in this speci*fi*c group of mutation carriers appears to be justi*fi*ed by our results. In patients with a *CDKN2A-p16-Leiden* mutation with cystic lesions between 10 and 20 mm, the screening interval might be shortened to 6 to 9 months or additional EUS might be performed. If cystic lesions show worrisome features, surgery is recommended. In view of the substantial size of PDACs detected at 1-year intervals, shorter screening intervals might be recommended for all patients, if further studies show this approach to be cost-effective.

Future studies should also address whether the known risk factors for PDAC such as smoking, body mass index, and a positive family history for PDAC are associated with an increased risk in high-risk groups. In a recent analysis of risk factors in our cohort of

CDKN2A-p16 mutation carriers, we found that smoking and a positive family history for PDAC were associated with an increased risk of PDAC, although the association was not statistically signi*fi*cant due to a lack of power.

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CHAPTER 4

4

Risk of multiple pancreatic cancers in CDKN2A-p16-Leiden mutation carriers

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Eur J Hum Genet 2018; 26: 1227-1229

Abstract

CDKN2A-p16-Leiden mutation carriers have a substantial risk of developing pancreatic ductal adenocarcinoma (PDAC). One of the main clinical features of hereditary cancer is the development of multiple cancers. Since 2000, we have run a surveillance program for CDKN2A-p16-Leiden mutation carriers. The patients are offered a yearly MRI with optionally endoscopic ultrasound. In patients with a confirmed lesion, usually, a partial resection of the pancreas is recommended. A total of 18 PDAC
(8.3%) were detected in 218 mutation carriers. In this report, we describe two CDKN2A-p16-Leiden patients with a synchronous and metachronous PDAC. Including two previously-reported cases, we identified four patients with multiple PDAC: two of 18 patients within the surveillance program (11%) and two patients with a proven CDKN2A-p16-Leiden mutation not participating in the surveillance program. In conclusion, this study demonstrated a high risk of developing multiple PDAC in CDKN2A-p16-Leiden mutation carriers. After detecting a primary tumor, it is very important to exclude the
presence of a second synchronous tumor. Moreover, after a partial pancreatectomy for PDAC, close surveillance is necessary. In view of the current findings, offering a total pancreatectomy might be an appropriate option in patients with an early PDAC.

Introduction

Hereditary factors account for 3–5% of all pancreatic ductal adenocarcinomas (PDAC) (1). In approximately 4% of familial PDAC, a cancer is caused by an underlying defect in genes including *BRCA2, CDKN2A, PALB2*, the mismatch repair (MMR) genes, and *STK11* (2). The lifetime risk of developing PDAC for carriers of a gene defect in *CDKN2A-p16-Leiden* is 15–20% (3).

One of the main features of hereditary cancer is the high risk of developing multiple (synchronous or metachronous) cancer. However, multiplicity might be masked in hereditary PDAC because most patients die within 6–12 months (4).

Recently, we described two patients with a *CDKN2A- p16-Leiden* mutation with metachronous PDAC (5, 6). In the current report, we describe two additional *CDKN2A-p16-Leiden* patients, one with a synchronous and one with a metachronous PDAC.

Patients and methods

Since 2000, we have run a surveillance program in the Leiden University Medical Center (LUMC) for individuals with a founder mutation in the *CDKN2A* gene, called *p16- Leiden* (NM_000077.4: c.225_243del19, p. (Ala76Cysfs*64)) (7). The program consists of annual magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), and, optionally, endoscopic ultrasound (EUS). In patients with a suspicious lesion, additional EUS and computed tomography (CT) scanning is performed within two to three weeks. If the lesion is confirmed by two out of the three modalities, surgery is offered. To avoid the serious morbidity associated with total pancreatectomy, until recently a partial resection of the pancreas was recommended. Acquired data was submitted to a public

CDKN2A gene variant database (https://databases.lovd.nl/shared/genes/CDKN2A; submission IDs # 00155215 and # 00155216).

Results

A total of 218 *CDKN2A-p16-Leiden* mutation carriers are under surveillance as of 01-04-2017. Since 2000, the screening program has detected PDAC in 18 patients (8.3%) and nine of these patients have since died from metastatic disease. The mean follow-up time for all 18 patients is 24.1 months (median follow-up: 17.5 months).

The first patient with multiple PDAC was a 67-year-old female carrier of a *CDKN2A-p16-Leiden* mutation that first entered MRI/MRCP pancreas surveillance in 2006. The patient had a sister who died of PDAC at the age of 52. She reports drinking 1–2 glasses of wine a week and has never smoked. In 2016, 11 months after a previous normal MRI scan, the patient presented with painless jaundice. A new MRI scan showed a 14-mm lesion in the head of the pancreas, which was confirmed by EUS. The patient underwent a pancreaticoduodenectomy, and histopathological examination of the surgical specimen showed a moderately differentiated PDAC of 13 mm, and one tumor-positive lymph node out of the 18 removed. After surgery, the patient was treated with gemcitabine and capecitabine. Regrettably, 6 months later, a yearly review of all MRI scans of patients in the surveillance program revealed that this patient had a second tumor in the corpus, which was confirmed by CT scanning. Subsequently, the patient underwent an uneventful completion of pancreatectomy. Pathological examination of the surgical specimen confirmed the presence of a 19-mm PDAC with no tumor- positive lymph nodes out of three removed. Molecular analysis of both lesions through Next Generation Sequencing (NGS) showed a class 5 variant in KRAS, NM_033360.2:c.34G>C, p.(Gly12Arg) and class 4 variant in *SMAD4*, NM_005359.5:c.353C>T, p.(Ala118Val) for the first tumor in the head, and a class 5 variant in KRAS, NM_033360.2:c.35G>T, p.(Gly12Val) together with a class 4 variant in *TP53*, NM_000546.5:c.517G>T, p. (Val173Leu) for the second tumor, besides the known p16-Leiden variant in *CDKN2A* (8).

Outside the surveillance program, a second patient with a proven *CDKN2A-p16-Leiden* mutation carrier at the LUMC was found to have a metachronous PDAC. This 57-year-old female underwent a Whipple operation due to an ampullary carcinoma 11 years back. She has never smoked or consumed alcohol. The family history revealed that her mother and maternal grandfather both had ampullary carcinomas previously. A maternal uncle and aunt, and the aunt's children have been diagnosed with melanoma. The patient was presented in March 2017 with liver and pulmonary metastases and a mass at the site of the anastomosis from the Whipple operation. The CA19.9 was >12,000. FNA biopsy showed a cancer of pancreaticobiliary origin. Molecular analysis using NGS of the ampullary carcinoma diagnosed 11 years ago revealed class 5 variant in KRAS, NM_033360.2:c.35G>A, p.(Gly12Asp) and the known *p16-Leiden* variant in *CDKN2A*.

In tumor cells collected by fine-needle aspiration (FNA) from the recently diagnosed tumor, NGS also showed the same class 5 variant in *KRAS* and the *p16-Leiden* 19 bp deletion. In addition, a class 5 variant was found in *TP53*, NM_000546.5:c.722C>T, p.(Ser241Phe), a class 3 *STK11* missense variant in NM_000455.4/NG_007460.2: c.598- 1G>A, and a deletion

of *SMAD4*, determined by copy number analysis. In view of the identification of the *p16-Leiden* variant, the observed partial differences in the gene variants between the two tumors and the long time-interval since the first cancer, the newly diagnosed tumor should be regarded as a second primary PDAC.
If we include the previously reported cases, we identified two *CDKN2A-p16-Leiden* patients with multiple PDAC out of the 18 screen-detected PDAC (11%), one with two synchronous PDAC and one with a metachronous PDAC. Two *CDKN2A-p16-Leiden* patients detected outside the program were both with metachronous PDAC.

Discussion

The present study indicates that multiple PDACs can be found in a substantial proportion (up to 11%) of *CDKN2A-p16-Leiden* mutation carriers. As most patients with hereditary PDAC die within 1 year, the real risk is probably much higher.
The risk of synchronous or metachronous cancers is a well-known phenomenon in inherited forms of cancer (9, 10). Owing to the current surveillance program for *CDKN2A-p16-Leiden* carriers, an increasing number of patients with PDAC are diagnosed at an early stage, resulting in a longer life expectancy (4). As a consequence, we expect to diagnose more patients with multiple tumors.

Our findings have immediate clinical implications. Firstly, after detection of a primary PDAC, it is very important to exclude the presence of a second synchronous tumor. As the identification of a second synchronous tumor in patients with sporadic PDAC is very unusual, a second tumor can be easily overlooked, as illustrated by one of the patients presented here. Secondly, in patients with hereditary PDAC undergoing partial resection of a primary tumor, close surveillance (e.g., at six month intervals) of the remaining pancreas is of utmost importance, as three of our patients developed a second PDAC (5, 6).
The most challenging question is whether we should now offer total pancreatectomy to all *CDKN2A-p16-Leiden* mutation carriers with primary PDAC. In patients with PDAC with poor prognostic indicators, a partial pancreatectomy is probably still the best option because expected survival is usually less than 2 years and a total pancreatectomy would substantially reduce the remaining quality of life. However, patients with a small lesion (<15 mm) and no evidence of lymph node metastases have a much better prognosis, and total pancreatectomy could be considered. A well-known disadvantage of the total pancreatectomy is the development of diabetes and the associated significant impairment of general quality of life (11). On the other hand, a disadvantage of a partial resection is that, even with intensive surveillance, the chance of detecting a second tumor at an early stage is limited. For *CDKN2A-p16* mutation carriers, a total pancreatectomy may therefore bring relief from the ongoing stress associated with the possibility of a second PDAC. Thus far, we have preferred to offer all patients with screen-detected PDAC a partial pancreatectomy and intensive follow-up after surgery. However, in view of the current findings, offering a total pancreatectomy might be an appropriate option in patients with early PDAC. We therefore suggest that all the pros and cons are discussed with a patient prior to surgery, resulting in a shared decision.

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CHAPTER 5

Cost-effectiveness of pancreas surveillance: the CDKN2A-p16-Leiden cohort

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United European Gastroenterology J 2023; 11: 163-170

Abstract

Background: *CDKN2A*-p16-*Leiden* mutation carriers have a high lifetime risk of developing pancreatic ductal adenocarcinoma (PDAC), with very poor survival. Surveillance may improve prognosis.

Objective: To assess the cost-effectiveness of surveillance

Methods: In 2000, a surveillance program was initiated at Leiden University Medical Center with annual MRI and optional EUS. Data were collected on the resection rate of screen-detected tumors and on survival. The Kaplan-Meier method and a parametric cure model were used to analyze and compare survival. Based on the surveillance and survival data from the screening program, a state-transition model was constructed to estimate lifelong outcomes.

Results: A total of 347 mutation carriers participated in the surveillance program. PDAC was detected in 31 patients (8.9%) and the tumor could be resected in 22 patients (71.0%). Long-term cure among patients with resected PDAC was estimated at 47.1% ($p<0.001$). The surveillance program was estimated to reduce mortality from PDAC by 12.1% and increase average life expectancy by 2.10 years. Lifelong costs increased by €13,900 per patient, with a cost-utility ratio of 14,000 euro per QALY gained. For annual surveillance to have an acceptable cost-effectiveness in other settings, lifetime PDAC risk needs to be 10% or higher.

Conclusion: The tumor could be resected in most patients with a screen-detected PDAC. These patients had considerably better survival and as a result annual surveillance was found to be cost-effective.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death. Most PDACs in patients who present with symptoms are diagnosed at an advanced stage and, as a consequence, only 15% of tumors can be resected. The 5-year survival rate of all PDAC patients is approximately 8% (1,2). At the present time, early detection and surgery is the only way to potentially cure this disease.

Hereditary factors play a role in the development of PDAC in 5-10% of all cases, with either a positive family history for PDAC or a recognized underlying gene defect associated with PDAC (3). During the last two decades, surveillance programs for individuals with an increased risk of PDAC have been implemented in many centers worldwide , resulting in higher curative resection rates and better survival (4-8).

Relatively few studies have investigated the cost-effectiveness of surveillance programs for individuals at increased risk of pancreatic cancer. The available studies concluded that pancreatic cancer screening is generally cost-effective in various high-risk groups (9-12). In the present study, we evaluate the cost-effectiveness of a surveillance program in the large cohort of *CDKN2A*-p16-*Leiden*-mutation carriers.

Patients and methods

Surveillance program and data collection

The surveillance program was initiated in 2000 at the Department of Gastroenterology & Hepatology, Leiden University Medical Center (4). Only patients with a proven *CDKN2A*-p16-*Leiden* founder mutation or other pathogenic variant were selected for the program. The surveillance protocol consists of an MRI once a year, with an optional EUS. In case of suspicion of a malignant lesion, the MRI is repeated within 3 months. In case of a highly suspicious lesion, an additional EUS and CT are performed within 2-3 weeks. If these modalities confirm the lesion, a partial pancreatectomy is performed. Most patients with PDAC are also offered chemotherapy.

The study was approved by the IRB of the Leiden University Medical Center (P00.107). All authors had access to the study data and reviewed and approved the final manuscript. All calculations were performed in Stata/IC 14.2 for Windows (StataCorp LLC, Texas, USA).

Survival analysis

Survival data have been reported recently (4). For the current analysis, we performed parametric survival analyses on these data to allow for extrapolation beyond the duration of follow-up. Survival after surgery among resected and non-resected patients was estimated using a cure model, i.e. a mixture of either cure from PDAC or Weibull-distributed survival (13). The cure probability was only maintained if the probability had a statistically significant non-zero value at $p \leq 0.05$. The same parametric model was used to estimate the time until detectable PDAC (14). Kaplan-Meier analysis was performed to validate the estimated parametric survival curves, with log-rank test to compare resected and non-resected patients.

Cost-effectiveness model

A state-transition model was constructed for the surveillance program and subsequent management of PDAC (Figure 1, Table 1). Patients are at risk for developing detectable PDAC (incidence rate λ) and dying (mortality rates μ_0, μ_1, μ_2). Patients with detectable PDAC are identified and treated surgically after a lead time (rate τ). When identified, patients may or may not be resectable (with probabilities π_1 and $1-\pi_1$). When resected, patients may or may not be cured (with probabilities π_2 and $1-\pi_2$).

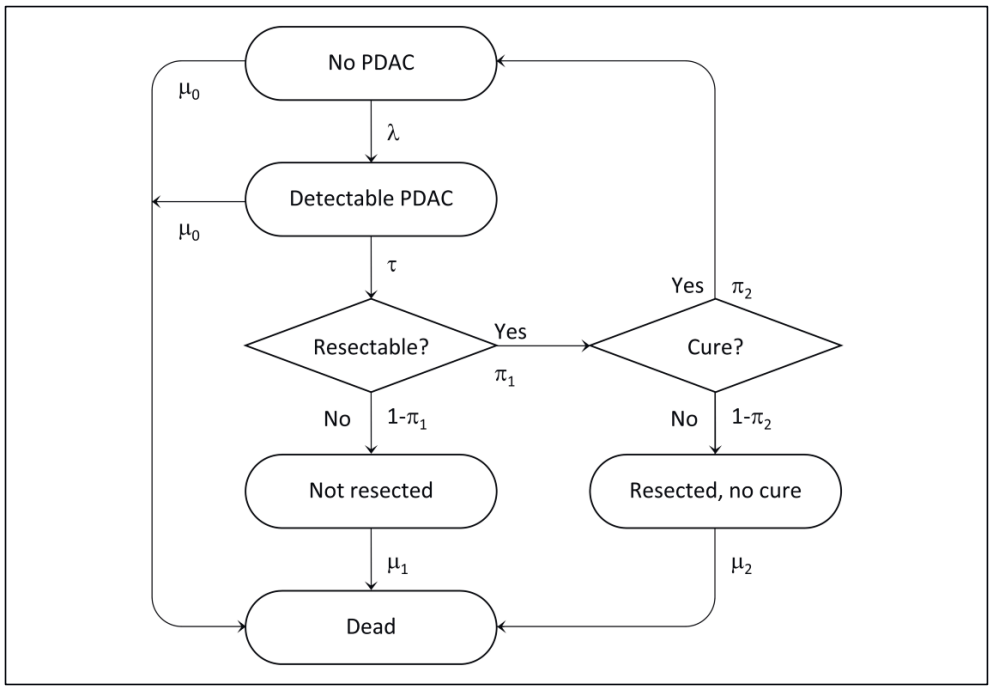

Figure 1. State-transition model for pancreatic cancer surveillance

Table 1. Parameters in the state-transition model

Parameter		Estimates and assumptions
λ	Incidence rate for detectable PDAC	mean = 76.5 yr (SD = 10.8)
	Age distribution:	truncated to only values below 75
τ	Lead time before PDAC is detectable	mean = 0.5 yr
	with surveillance:	mean = 1.0 yr
	without surveillance:	
π_1	Probability that detected PDAC is resectable	π_1 = 71.0% (95% CI 54.0% to 87.9%)
	with surveillance:	π_1 = 15% [18]
	without surveillance[25][25][25][25][25][25][25][25][25][25][25][25][25][25][25]:	
π_2	Probability that resected patient is cured	π_2 = 47.1% (95% CI 25.1% to 69.1%)
	with surveillance:	π_2 = 0% [8]
	without surveillance[26][26][26][26][26][26][26][26][26][26][26][26][26][26][26]:	
μ_0	Mortality rate without detected PDAC	mean = 84.5 yr (SD = 10.8)
	Female life expectancy:	mean = 81.5 yr (SD = 10.7)
	Male life expectancy:	
μ_1	Mortality rate after non-resected PDAC	mean = 1.10 yr (SD =0.65)
	Life expectancy:	
μ_2	Mortality rate after resected non-cured PDAC	mean = 1.90 yr (SD =0.76)
	Life expectancy:	

The model was used to simulate individual patient histories, both with and without a surveillance program (15). Each simulated history started at age 45, for either a female or a

male individual. First, survival time without PDAC was simulated based on national Dutch survival data, assuming a Weibull distribution fitted to the mean and SD as obtained from the life tables of Statistics Netherlands (16,17). Secondly, for the annual surveillance policy, the time until detection of PDAC and resectability of the tumor were estimated from the surveillance data of the surveillance program (14,4). No further surveillance for PDAC was assumed beyond 75 years of age and after a first PDAC. The survival time after PDAC was simulated from either the estimated cure model for resected patients or the estimated Weibull distribution for non-resected patients. Overall lifetime was then estimated as the minimum of the survival time without PDAC and the survival after PDAC. Thirdly, the policy without surveillance program was modeled to have a longer lead time before PDAC is detected. Due to lack of data, we assumed exponentially-distributed lead times between the origin and detection of PDAC. Moreover, without a surveillance program, detected PDAC was assumed to be resectable with probability π_1=15% (18), and curable with probability π_2=0 (8).

QALYs and costs

For each simulated patient history, we estimated lifetime costs and quality-adjusted life years (QALYs). QALYs were estimated using utility values obtained from the literature. For utility without PDAC, with undetected PDAC and after cured PDAC we used a utility value of 0.85, based on the Dutch EQ-5D valuations above age 40 (19). For utility after non-resected PDAC and after non-cured resected PDAC we used a utility value of 0.75, based on a reported range from 0.72 to 0.78 for EQ-5D values in representative publications (20-25).

Costs were assessed from a healthcare perspective (Supplementary Table), including only healthcare associated with PDAC surveillance (visits, MRI, EUS, and CT), PDAC treatment (surgery and chemotherapy) and follow-up after diagnosis (visits). Prices of healthcare were obtained from Dutch national averages as reported by hospitals (n=45 out of 84, www.ziektekosten.nl), or otherwise from benchmark costs for Dutch university medical centers (n=4 out of 8, www.performation.nl). Costs are reported at 2022 price level. Costs and QALYs over time were discounted at 4% and 1.5%, respectively, in accordance with Dutch guidelines for economic evaluations in healthcare (26).

Cost-effectiveness analysis

Model outcomes were estimated by averaging 10,000,000 simulated patient histories, which was sufficient to reduce the half-width of the 95% confidence interval to at most one unit of the last reported decimal.

Sensitivity analyses were performed for lifetime PDAC risk (±50%, by changing the incidence rate), cure probability (over the 95% CI), discount rate for costs (0% to 5%), surveillance costs (±50%), treatment costs (±50%), lead time without surveillance (range 0.5 to 2 years), utility after PDAC (±0.10), and starting age (range 45 to 70).

We also modeled two surveillance programs with a shorter (i.e., biannual) screening interval. In program 1, we assumed that with biannual screening the annual surveillance costs would double and resectability would improve to 90%. In program 2, we additionally assumed that cure after surgery would improve to 70%. Cost-effectiveness for these programs was calculated as compared to annual screening.

In the Netherlands, a willingness-to-pay threshold of 80,000 euro per QALY is recommended by the Dutch Council for Public Health and Health Care for conditions with a high disease

burden, like diagnosed PDAC. For low disease burden and prevention, a lower threshold of 20,000 euro per QALY is used. In the current paper we will consider cost-effectiveness acceptable for cost-utility ratios up to an intermediate threshold of 50,000 euro per QALY (27).

Results

A total of 347 mutation carriers were included in the study, of whom 201 were female (57.9%). The median age at start of surveillance was 49 years (IQR 44 to 55 years), with a median follow-up time of 6 years (IQR 2 to 10 years, range 0 to 17 years). A total of 31 (8.9%) primary PDAC were detected by the screening program, of which 20 in female patients (65%). The median age at diagnosis was 60 years (range 39 to 74 years). The tumour could be resected in 22 patients (71.0%). Extensive details have been reported before (4).

Survival analysis

The Kaplan-Meier survival curve (Figure 2) was significantly better among patients with resected PDAC than with non-resected PDAC (p<0.001, median 36 versus 16 months).

The parametric survival curves provided a close visual fit to the Kaplan-Meier curves. For resected patients, the long-term cure probability was estimated at 47.1% (p<0.001, 95%CI 25.2% to 69.1%). Among the resected but non-cured patients, average survival time was 23 months. Among patients with non-resected tumor the average survival time was 13 months.

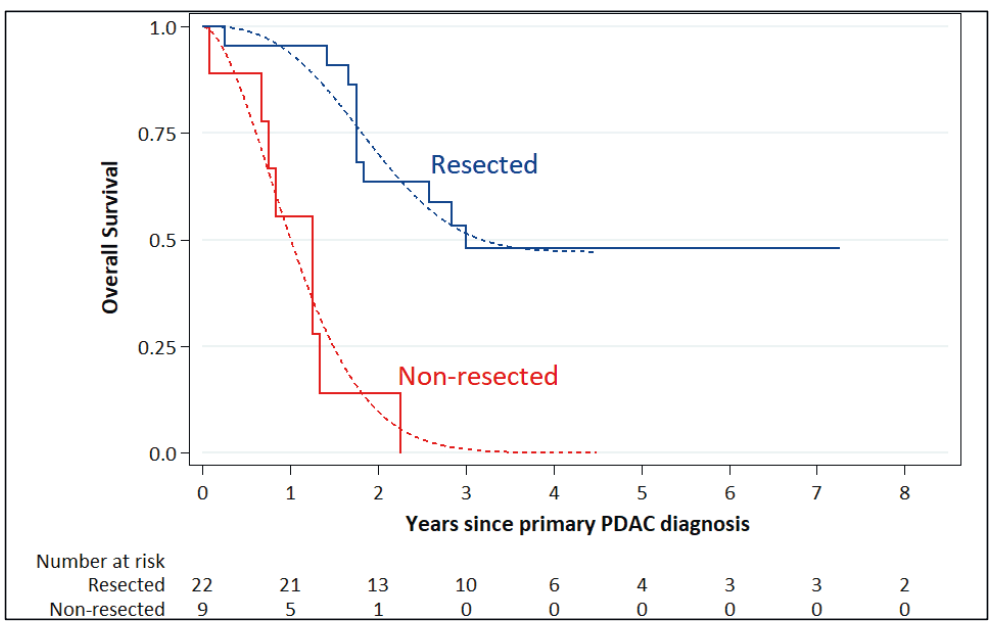

Figure 2. Estimated parametric survival distributions (dashed lines) among resected (n=22) and nonresected (n=9) PDAC patients, in comparison to Kaplan-Meier curves

Cost-effectiveness analysis

Patient outcomes with and without the surveillance program are shown in Table 2. With surveillance the lifelong probability of a PDAC diagnosis is slightly higher, because without surveillance some patients die before diagnosis. More importantly, with surveillance the majority of patients (71.0%) with PDAC are diagnosed at a resectable stage and about one in three of diagnosed patients (33.5%) is estimated to have long-term cure after surgery. As a result, mortality from PDAC is estimated to decrease by 12.1%, life expectance increases by 2.10 years, and quality-adjusted life years by 0.97 years.

Nevertheless, screening does come with additional costs. The lifelong healthcare costs for patients undergoing surveillance were estimated at €15,400, compared to only €1,500 without surveillance. Of the cost difference, 82% is due to surveillance costs. Although treatment costs are also substantial, they apply to only part of the population and receive less discounted weight because they occur on average more than 20 years in the future. Cost-effectiveness ratios are estimated at 115,000 euro per prevented PDAC death or 14,000 euro per QALY gained.

Table 2. Average lifelong outcome with and without MRI surveillance from age 45-75 years, for a 45-year-old person in the CDKN2A-p16-Leiden population

Outcome parameter	Surveillance	No surveillance	Difference
Lifetime probability of diagnosed PDAC	37.6%	37.3%	0.3%
of which non-resected	29.0%	85.0%	-56.0%
resected, non-cured	37.5%	15.0%	22.5%
resected, cured	33.5%	0.0%	33.5%
Mortality from PDAC	24.3%	36.4%	-12.1%
Age at PDAC diagnosis	66.40 yr	66.90 yr	-0.49 yr
Life years	33.74 yr	31.64 yr	2.10 yr
QALYs	21.76 yr	20.79 yr	0.97 yr
Costs of screening (in €)	11,400	0	11,400
Costs of surgery (in €)	3,100	700	2,400
Costs of chemotherapy (in €)	700	700	0
Costs of follow-up after PDAC (in €)	200	100	100
Costs in total (in €)	15,400	1,500	13,900
Cost-effectiveness ratio	115,000 euro per prevented PDAC death		
Cost-utility ratio	14,000 euro per QALY gained		

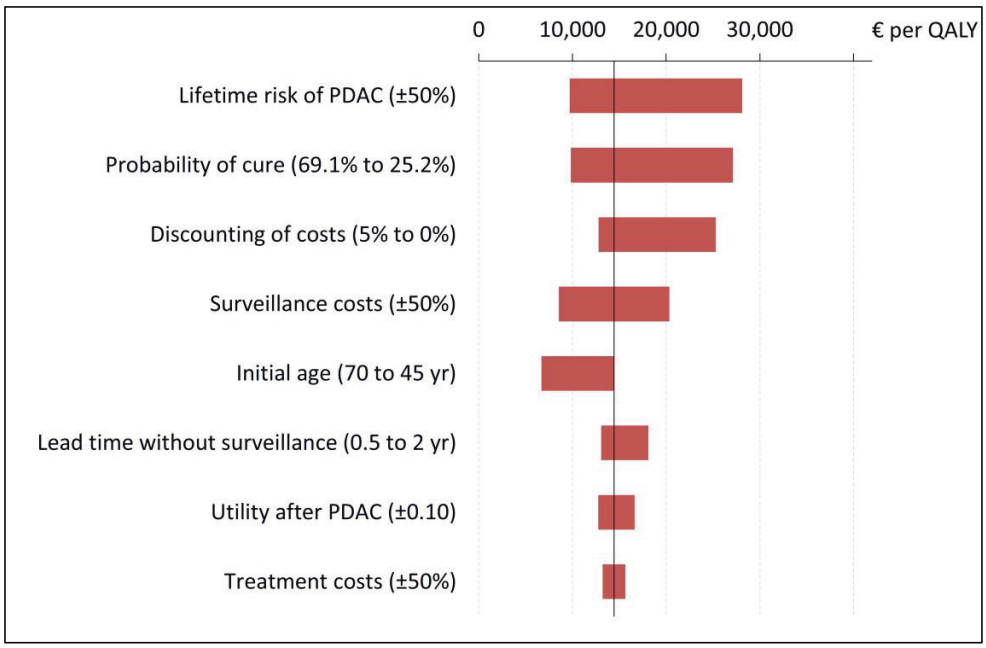

Figure 3. Tornado diagram, showing the impact of model parameters on the estimated cost-effectiveness of annual surveillance

Sensitivity analyses

In all sensitivity analyses cost-effectiveness remained below 30,000 euro per QALY (Figure 3), which is well below the acceptability threshold of 50,000 euro per QALY. The most influential variables were the lifetime risk of PDAC and the probability that surgery results in long-term cure. Figure 4 shows how lower PDAC risk results in worse cost-effectiveness. For annual surveillance to have an acceptable cost-effectiveness below 50,000 euro per QALY, lifetime PDAC risk needs to be 10% or higher.

The figure also shows the estimated cost-effectiveness of more expensive bi-annual surveillance. The first program is bi-annual surveillance with improved 90% resectability (instead of the 71.0% for annual screening), but without improved cure among resected patients. This program 1 will only be cost-effective for a lifetime PDAC risk of at least 32%. The second program, in addition, improves cure to 70% (instead of 47.1%). The cost-effectiveness of this program 2 will be very similar to annual surveillance, with about double the costs but also about double the QALY gain.

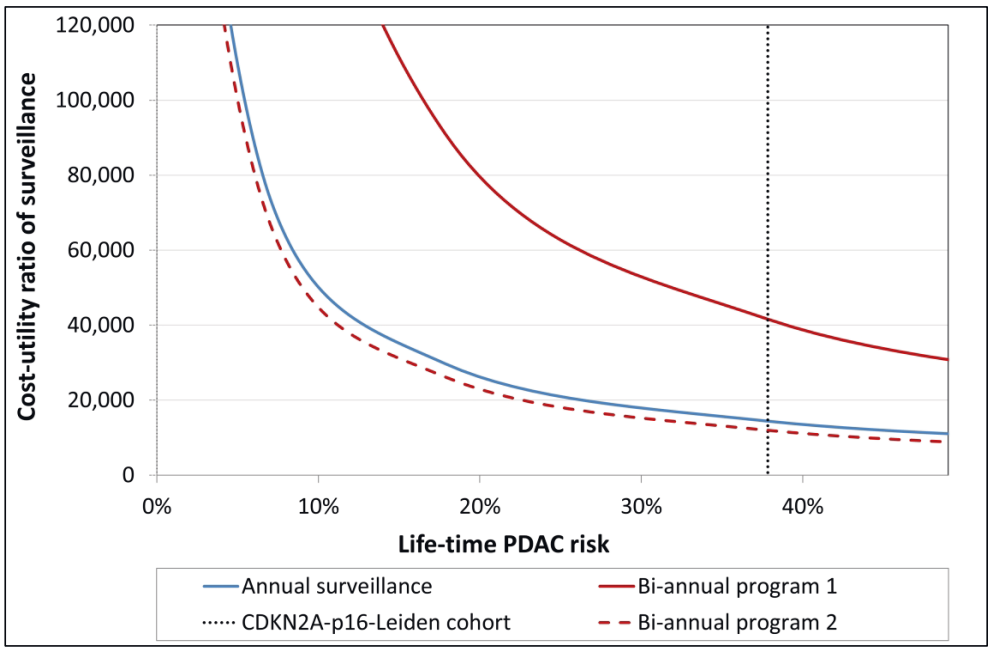

Figure 4. Estimated cost-utility ratio of annual and bi-annual pancreas surveillance, depending on the lifetime PDAC risk in the population

Discussion

In the current study we evaluated the cost-effectiveness of a surveillance program aimed at *CDKN2A*-p16-*Leiden*-mutation carriers. Of the 347 mutation carriers, 31 individuals (8.9%) developed PDAC and the tumor was resectable in 22 cases (71.0%). The long-term survival rate for patients with resected PDAC was estimated at 47.1%, compared to 0% for patients with a non-resected tumor. Cost-effectiveness of annual surveillance was estimated at a very acceptable 14,000 euro per QALY.

Over the last two decades, interest for surveillance amongst individuals at high-risk of pancreatic cancer has increased substantially. Following the identification of a large cohort of carriers of a *CDKN2A* founder mutation close to Leiden University Medical Center, we initiated MRI-based pancreas surveillance in 2000. In previous studies (14,18) we reported a high PDAC detection rate, confirming the high-risk of developing PDAC previously calculated for these carriers (28,29), and our most recent study reported improved survival, although the number of screen-detected PDACs was relatively small (14). In the current study, which now includes a substantial number of screen-detected PDACs (4), we can confirm the high resection rate and better survival.

As the surveillance program involves use of relatively expensive screening tools, it is important to understand its cost-effectiveness. To date, four studies have addressed the cost-effectiveness of surveillance for individuals at risk for PDAC. Although all reports showed that PDAC surveillance was cost-effective, the populations analyzed (FPC, carriers of various

mutations associated with PDAC development), the screening strategies (once in a lifetime, annual or bi-annual screening) and screening methods (EUS or MRI/MRCP) varied widely between the studies. One study also constructed a decision tree model for a hypothetical familial pancreatic cancer (FPC) population that underwent one-time screening using EUS (9). The investigators concluded that for screening to be cost-effective the probability of dysplasia needs to be sufficiently high and the screening method must be sufficiently sensitive. Another study developed a screening protocol that consisted of a bi-yearly MRI (10) using data that were based on a literature search for various high-risk individuals (e.g. Peutz-Jeghers syndrome, hereditary pancreatitis, FPC, *CDKN2A*-p16-*Leiden* and new-onset diabetes > age 50 with weight loss or smoking) (10). MRI screening was affordable for HRI individuals, although the authors also stated that the substantial costs of screening for asymptomatic individuals influence compliance because some or all of the costs of screening are not covered by healthcare systems in the United States (in contrast to the Dutch healthcare system). A third study from Denmark reported the outcome of surveillance in a cohort of individuals with FPC and hereditary pancreatitis (HP) and calculated the related costs of surveillance (11). They concluded that surveillance was most cost-effective in patients with FPC. The most recent study used a Markov model and compared various strategies including no surveillance, surveillance using MRI and surveillance using EUS (12). This study found that MRI surveillance was most cost-effective for individuals with a moderately increased risk of PDAC and surveillance based on EUS was the most cost-effective strategy for individuals with a more than 20-fold increased risk.

In the current study, the cost-effectiveness of annual surveillance was estimated at 14,000 euro per QALY, an estimate that is likely to be acceptable in most countries. We observed that several variables in particular influenced our study results. One important factor was the elevated genetic risk of our patient cohort, as *CDKN2A*-p16-*Leiden*-mutation carriers show a model-estimated lifetime PDAC risk of 37.6%. We estimated that surveillance could be cost-effective for populations with a lifetime risk of at least 10%. This figure matches earlier studies using hypothetical simulation models which suggested that pancreas screening is ineffective in the general population but effective in patients with a substantial risk (26,30,31). Screening of low-risk individuals was associated with a reduced life expectancy, an outcome attributed to the increased discovery of insignificant lesions and subsequent unnecessary surgical intervention. As an international consortium of experts currently recommends pancreatic surveillance for HRIs with an estimated lifetime risk of PDAC of >5% (32), more studies are needed to assess the cost-effectiveness of surveillance of individuals with a relatively low risk (i.e., <10%).

The other key factor in cost-effectiveness was the ability of the surveillance program to detect PDAC at an earlier stage, which resulted in a considerable increase in patients with resected PDAC (from 15% to 71.0%). Furthermore, a substantial proportion (47.1%, $p<0.001$) of these patients show long-term cure. Without this observed cure, it would be difficult to exclude the possibility that improved survival due to surveillance was simply due to lead time bias (whereby improved survival after diagnosis is due to earlier diagnosis rather than longer survival). Under the current surveillance program an estimated 33.5% of diagnosed patients are considered cured, which is enough for the program to be cost-effective. Nevertheless, a few patients developed an advanced cancer within the recommended annual surveillance interval of the current program (4). Shorter intervals might therefore be considered in

individuals with additional risk factors for development of PDAC (e.g., smoking, strong family history for PDAC). The sensitivity analysis indicated that bi-annual surveillance could be cost-effective, if it further improved the probability of cure after surgery.

Our study had both strengths and limitations. All previous cost-effectiveness studies, except the study from Denmark, were based on hypothetical models. An advantage of the current study is that we used real data from our 347 participants with a *CDKN2A*-p16-*Leiden*-mutation collected over two decades. A limitation of our study is that the conclusions may not be representative for patients at risk for PDAC in other contexts (e.g. chronic pancreatitis). Similarly, we used costs specific to the Dutch healthcare system, which may not be representative of other countries. A second limitation is that for ethical reasons there was no control group of patients not under surveillance. Data on natural history were therefore derived from historical controls with symptomatic PDAC known at the Dutch FAMMM registry (18). And thirdly, several simplifying assumptions needed to be made for which limited or no evidence was available, including assumptions on utilities, lead times and other risks in this population. In particular, we assumed that neither surveillance nor a new PDAC occurs beyond the age of 75, as we have not observed a case in our cohort. However, we note that the incidence rate increases with age and therefore suggests that longer follow-up is needed to assess the cost-effectiveness of surveillance at older ages.

In conclusion, this study demonstrated that screening for PDAC is cost-effective for *CDKN2A*-p16-*Leiden*-mutation carriers. In most patients a screen-detected PDAC could be resected and these patients subsequently benefited from considerably better survival.

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CHAPTER 6

Incidental findings in pancreas screening programs for high-risk individuals: results from three European expert centers

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United European Gastroenterology Journal 2019; 7: 682-688

Abstract

Background: Widespread abdominal imaging has led to a substantial increase in the detection of incidentalomas. Currently, an increasing number of centers offer surveillance of the pancreas to individuals at high risk (IARs) of pancreatic ductal adenocarcinoma (PDAC).
Objective: The aims of this study were to evaluate the frequency and type of incidental findings in a magnetic resonance imaging (MRI)-based surveillance program for IARs for PDAC, and to discuss the benefit of detecting these lesions.
Methods: The outcome of MRI screening was reviewed in 568 individuals from three long-term pancreas surveillance programs conducted at three large European expert centers. All MRIs were studied in detail for the presence of incidental lesions.
Results: The most common lesions were liver cysts, renal cysts and liver hemangioma, which together comprised 75% of all lesions. Only five (0.9%) patients underwent surgery for a benign lesion. Cancer was detected in 11 patients (1.9%); early detection of tumors was beneficial in at least five cases.
Conclusion: The present study demonstrates that extrapancreatic incidentaloma is a common finding in IARs for PDAC, but rarely requires additional treatment. CDKN2A-p16-Leiden mutation carriers were the only patient group found to harbor a substantial number of cancers, and detection resulted in benefit in several cases.

Introduction

The widespread use of magnetic resonance imaging (MRI) and computed tomography (CT) has led to a substantial increase in the detection of incidental findings, more commonly referred to as incidentalomas. The most frequent and extensively described incidentalomas found with abdominal imaging are adrenal masses, liver cysts and renal cysts. The clinical significance of these lesions is often unknown. The management of an incidentaloma depends on the site, size and type of the lesion. Several guidelines have been published with detailed recommendations for management of these lesions (1-5). Experience has shown that with additional imaging and subsequent surgical intervention, most lesions prove to be benign. Currently, an increasing number of centers offer surveillance of the pancreas to individuals at high risk (IARs) of pancreatic ductal adenocarcinoma (PDAC), usually involving MRI and/or endoscopic ultrasonography (EUS) (6-9). These IARs can be subdivided into two groups: (1) patients with an underlying gene defect associated with a high risk of PDAC, most commonly BRCA2 or CDKN2A mutations, and (2) patients with a positive family history of PDAC, also known as familial pancreatic cancer (FPC). Detection of extrapancreatic incidental lesions in these high-risk groups may offer benefit if the lesion is (pre)malignant. However, if only benign lesions are found, additional imaging and surgical intervention might be a burden, especially in high-risk groups that already undergo surveillance for multiple cancers.

In the present study, we evaluated the frequency of extrapancreatic incidentalomas in large, long-term, prospective surveillance programs for PDAC at three European expert centers. The aims of this study were (1) to evaluate the occurrence and type of extrapancreatic incidental findings in these surveillance programs, and (2) to assess the benefit of detecting these lesions.

Methods

The current study was made possible through the collaboration of three tertiary referral centers: the Department of Surgery at Philipps University in Marburg, Germany, the Department of Medical Oncology at Ramon y Cajal University Hospital in Madrid, Spain, and the Department of Gastroenterology & Hepatology at Leiden University Medical Center in Leiden, The Netherlands. The study design was a retrospective evaluation of an ongoing prospective follow-up study (7,8,10). In Leiden, a surveillance program was initiated for carriers of a CDKN2A-p16-Leiden mutation in the year 2000. In Marburg a similar program was introduced, mainly for families with FPC, in 2002. In 2010 a surveillance program was initiated in Madrid for various high-risk groups. The surveillance tools included MRI and EUS of the pancreas. The total number of individuals, the characteristics of the various high-risk groups and the surveillance methods implemented at each center are summarized in Table 1.

All MRIs were studied in detail for the presence of incidental findings including cysts, solid lesions, focal nodular hyperplasia (FNH), hemangioma and cancers. For all patients with an incidental lesion, further information was collected on whether additional imaging, intervention or surgery was performed. The observation time was from the start of a screening program up to 1 January 2018. The study was approved by the ethics committees of the respective centers. Oral or written informed consent was received from all patients. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Table 1. Characteristics of participants (n ¼ 568) in pancreas surveillance programs in three European expert centers.

	Leiden	Madrid	Marburg
Year started surveillance	2000	2010	2002
FPC	–	52	240
FDR with PC < 50	–	5	–
HBOC	–	19	–
BRCA1 or 2 mutation carrier	–	1	14
Lynch syndrome	–	1	–
Familial adenomatous polyposis	–	-	1
STK11-mutation	–	–	2
CDKN2A-p16-Leiden mutation	217	2	4
PALB2-mutation	–	–	7
FPC/Lynch Syndrome/HBOC	–	1	–
FPC/HBOC	–	2	–
Surveillance protocol	MRI with optional EUS since 2012	Annual MRI and EUS	Annual MRI and EUS every three years
Total number of IARs	217	83	268

EUS: endoscopic ultrasound; FDR: first-degree relative; FPC: familial pancreatic cancer; HBOC: hereditary breast ovarian cancer; IARs: individuals at high risk; MRI: magnetic resonance imaging; PC: pancreatic cancer.

Results

Leiden, the Netherlands

Of the 217 IARs under surveillance in Leiden during the study period, 214 were carriers of a

CDKN2A-p16-Leiden mutation while three had a pathogenic variant in CDKN2A. Ninety-four were male (43.3%) and 123 (56.7%) female. The mean age at start of surveillance was 51.5 years (range, 36.2–72.2 years), with a median follow-up time of 4.7 years (range, 0.0–16.9 years). A total of 117 extrapancreatic findings were observed, most frequently in the liver, including cysts (29%), adenoma/FNH (9%) and hemangioma (21%) (Table 2). One patient underwent an additional ultra-sonography and a fine-needle aspiration–biopsy because of a suspected lesion in the liver that proved to be an FNH.

Incidentalomas in the adrenal glands (adrenaloma) were identified in 12 cases (10.3%). In two of the 12 cases the lesion was removed during pancreatic surgery for a solid lesion. The first patient was a 40-year-old homozygote p16-Leiden carrier with a solid lesion in the uncinate process of the pancreas, together with a mass in the right adrenal gland detected on the first MRI. CT confirmed both lesions and defined the adrenal mass as an adrenaloma of 3.5 cm. A pancreaticoduodenectomy was performed and the adrenal mass was resected. Pathological examination revealed a PDAC and an adrenal adenoma without evidence of malignancy.

The second patient was a 66-year-old woman who came for her first MRI scan. The MRI showed a mass in the adrenal gland of 2.4 cm, together with a 1 cm hypovascular mass in the uncinate process. Subsequent CT confirmed both lesions but could not define the adrenal mass. The patient underwent a pancreaticoduodenectomy and an adrenalectomy. Pathological examination showed an intraductal papillary mucinous neoplasm with low-grade dysplasia, and an adrenaloma of 2.4 cm with adrenocortical hyperplasia.

Other frequently detected lesions are shown in Table 2. In seven cases (3.2%) various cancers were found outside the pancreas including two renal cell carcinomas, one colorectal cancer (CRC), a neuroendocrine carcinoma in the liver, a stromal tumor in the stomach and metastases of breast cancer and melanoma. Details of these findings are summarized in Table 3. In four of these patients the early detection of cancer was beneficial.

Table 2. Total number of incidental extrapancreatic lesions

Lesions	Leiden	Madrid	Marburg	Total (%)	
Hemangioma liver	25	5	25	55	(12.0%)
Adenoma/FNH liver	10	-	3	13	(2.8%)
Cyst liver	34	36	100	170	(37.0%)
Cyst kidney	17	24	75	116	(25.3%)
Cyst breast	2	-	1	3	(0.7%)
Adrenal lesion	12	2	12	26	(5.7%)
Aortic aneurysm	3	-	-	3	(0.7%)
Cancer	7	-	4	11	(2.4%)
Other lesions	7	55	-	62	(13.5%)
Total number of lesions	117	122	220	459	(100%)

Madrid, Spain
Eighty-three IARs were under surveillance, consisting of 37 men (44.6%) and 46 women (55.4%). The analyzed cohort included a number of high-risk groups. Forty-two belonged to FPC families, five individuals had a first-degree relative with PDAC younger than 50 years, 19 belonged to a hereditary breast ovarian cancer (HBOC) family, one individual was a BRCA2 carrier, one belonged to a Lynch syndrome family, two had a CDKN2A-p16-Leiden mutation, one belonged to a family with evidence of combined FPC, Lynch syndrome and HBOC, and two belonged to a family with mixed FPC/HBOC. The mean age at start of surveillance was 50 years (range, 29–81 years), with a median follow-up time of 2.9 years (range, 0.1–6.7 years). In total, 122 incidental lesions were detected in 83 individuals (Table 2). Liver cysts (29.5%) were the most commonly found lesions and renal cysts were the second most common finding (19.7%).

In none of the patients was surgical management required. There was one patient who required additional imaging after a solid renal tumor was found (0.8%), but the lesion was characterized as an angiolipoma.

Marburg, Germany
Of the 268 IARs under surveillance in Marburg during the study, 109 were men (40.7%) and 159 were women (59.3%). Average age at start of screening was 48 years (range, 25–75 years) and the median follow-up time was three years (range, 0.1–14.6 years). The cohort included 240 individuals with FPC, four BRCA1 mutation carriers, 10 BRCA2 carriers, seven PALB2 mutation carriers, four CDKN2A/p16-Leiden mutation carriers, two STK11 mutation carriers and one patient with familial adenomatous polyposis with PDAC. A total of 220 lesions were identified in the 268 patients (Table 2). The most common findings were cysts in the liver (45.5%) or kidney (34.1%). Adrenaloma were observed in 12 cases (5.4%). Liver cysts in two patients and a renal cyst in one patient (1.1% of all patients) required surgical removal.

Regarding the need for additional investigations, the two patients who had surgery for liver lesions had an additional contrast-enhanced ultrasonography. Another 47-year-old man had an additional gastroscopy because EUS gave a suspicion of a MALT (mucosa-associated lymphoma tissue) lymphoma, which was a peptic ulcer. In a 43-year-old woman, a mammography was performed because MRI showed contrast-enhancing lesions in both breasts. Mammography diagnosed fibroadenomas. In another 51-year-old female patient, a 53 50 mm solid liver lesion on MRI was further evaluated by contrast-enhanced ultrasonography, which confirmed a hemangioma.

Table 3. Characteristics of extrapancreatic cancers (or metastatic disease) detected by the Leiden program for PDAC.

Patient no.	M/F	Type of cancer (detected at first screening or during follow-up)	Age at diagnosis (y)	Year of diagnosis	Incidental MRI findings	Stage	Treatment	Status at 1 January 2018 (alive/dead/cause of death)
1	F	Metastases of BC (follow-up)	57	2011	Pleural effusion due to metastatic BC	Metastatic disease	Chemotherapy	Died 2015 of metastatic BC
2	F	Grawitz tumor (follow-up)	60	2014	Left lower kidney mass of 2.3 cm	Fuhrman grade 2, no metastasis, no angioinvasion, cutting edges free	Nephrectomy	Alive
3	M	NEC, primary site unknown (follow-up)	58	2016	Mass in left liver lobe of 53 mm	Metastasized NEC	No treatment possible	Died 2016 of aggressive NEC with metastases in adrenal gland, liver, lungs and bones
4	F	Tubulocystic renal cell carcinoma (first screening)	46	2016	Left kidney lesion with thick walls and septae of 3.4 cm	Grade 3	Nephrectomy	Alive
5	M	GIST (follow-up)	65	2016	Growth of a submucosal lesion in stomach	T2N0M0	Local wedge resection	Alive
6	M	Metastases of melanoma (follow-up)	59	2009	Ascites, peritoneal masses and two hypervascular lesions in liver	Metastatic disease	Chemotherapy	Died 2010, after initial good response on chemotherapy; developed secondary intradural metastases
7	M	Liver metastases of sigmoid carcinoma (follow-up)	56	2014	Two liver lesions	Liver metastases	Sigmoid resection and hepatectomy with neoadjuvant chemotherapy	Alive

BC: breast cancer; F: female; GIST: gastrointestinal stromal tumor; M: male; MRI: magnetic resonance imaging; NEC: neuroendocrine carcinoma; PDAC: pancreatic ductal adenocarcinoma; y: years.

Table 4: Charateristics of extra-pancreatic cancers (or metastatic disease) detected by the German program for PDAC

Patnr.	M/F	Type of cancer (detected at first screening or during follow-up)	Age at diagnosis	Date of diagnosis	MRI Findings	Stage	Treatment (resection, chemo?)	Status at 1-1-2018 (alive/dead/ cause of death)
1	f	multiple bone metastases of breast cancer (during follow-up)	55y	BC in 2004, metastases detected in 2016	Contrast enhancing lesions of the right ileum and lumbar spine	metastatic	Chemotherapy	Alive with disease
2	f	Klatskin tumor (follow-up)	60y	2011	Growing liver lesion, cholestasis, periportal edema	Bismuth IIIa	Trisecterectomy	Died 2 weeks postoperative due to liver failure
3	f	multiple liver and bone metastases of breast caner (first screening)	47y	BC in 2014, metastases detected in 10/2015 (bone) and 05/2016 (liver)	Multiple new and growing liver lesions, multiple new and growing lesions of the thoracic and lumbar spine	Metastatic disease	Chemotherapy	Alive with disease
4	m	Renal cell carcinoma (first screening)	52y	2015	Partially cystic cortical lesion of the left kidney with thick walls (15mm)	pT1a, N0, M0, L0, V0, G2, R0	Local resection	Alive without evidence of disease

Discussion

The present study shows that MRI-based pancreas surveillance programs for PDAC result in the detection of a large number of incidental lesions. The most commonly found lesions were liver cysts, renal cysts and liver hemangioma, which together accounted for 74% of all incidental lesions, followed by adrenal incidentaloma in 6% of patients. Only five (0.9%) patients underwent surgery for a benign lesion: two patients for a liver cyst, one for a renal cyst and two for an adrenal incidentaloma.

Cancer was detected in 11 patients (1.9%), including seven CDKN2A-p16-Leiden mutation carriers, and metastatic disease was detected in six of the 11 patients. Early detection of tumors was beneficial in at least five of the patients.

Several studies have reported frequencies of incidental findings detected during abdominal imaging. One study reported the rate of incidental findings of whole-body MRI in 148 healthy control participants (11). The most frequently found abnormalities were renal cysts (42.9%), gallstones (12.2%) and liver cysts/hemangioma (10.2%). In a similar study whole-body MRI was performed in 118 healthy individuals (12). A total of 106 incidental lesions were found in the 83 individuals with an abnormality, the most common lesions being renal cysts (16.0%), liver hemangioma (12.3%) and liver cysts (11.3%). These findings are in agreement with our findings for benign lesions. However, the rate of incidentally detected cancers in the

subgroup of CDKN2A-p16-Leiden mutation carriers was much higher.
What was the benefit of the detection of incidental lesions in our study? Although incidental findings were frequent, only 0.9% of the total group of IARs underwent a surgical intervention for a lesion, which was then found to be benign in all cases. A primary cancer, metastases of a previous cancer or a new cancer was detected in 1.9%. By contrast, in the Leiden cohort of CDKN2A-p16-Leiden mutation carriers, extrapancreatic cancer was detected in a substantial proportion of patients (seven patients out of 217 (3.2%)). The early detection of cancers in seven mutation carriers allowed curative resection of renal cancers in two patients, a gastric stromal tumor in one patient and colonic resection (and early start of chemotherapy) in one patient with CRC. In the German cohort, the detection of a renal cell carcinoma allowed curative resection. In addition, the identification of metastatic breast cancer in two patients allowed the early start of chemotherapy.
Strengths of the current study include the substantial size of the study group, the wide variation of high-risk groups and the long follow-up time. A possible limitation was that we are not informed about which definitions were used for a significant incidentaloma in the three expert centers and which guidelines for their management.

What are the clinical implications of our findings? First, it is important to inform all participants at the start of the surveillance program about the possibility of detecting incidental lesions. Based on our findings, it might be explained to patients that lesions are almost always harmless and will not require additional treatment. However, carriers of a CDKN2A-p16-Leiden mutation should be told that cancer might be detected outside the pancreas in a small proportion of patients.

To improve the investigation of the pancreas, there is currently a trend toward restricting MRI scanning to the pancreas only. However, to avoid missing cancers located outside the pancreas in CDKN2A-p16-Leiden mutation carriers, MRI assessment should include at least one scan of all abdominal organs.

In summary, the present study demonstrates that incidentaloma is a common finding in IARs for PDAC, but rarely requires additional treatment. CDKN2A-p16-Leiden mutation carriers were the only patient group found to harbor a substantial number of cancers, and detection resulted in benefit in several cases.

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CHAPTER 7

Dillemmas in the management of screen-detected lesions in patients at high risk for pancreatic cancer

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Fam Cancer 2017; 16:111-115

Abstract

In 3–5 % of all cases of pancreatic ductal adenocarcinoma (PDAC), hereditary factors influence etiology. While surveillance of high-risk individuals may improve the prognosis, this study describes two very different outcomes in patients with screen-detected lesions. In 2000, a surveillance program of carriers of a CDKN2A/p16-Leiden-mutation consisting of annual MRI was initiated. Patients with a suspected pancreatic lesion undergo CT-scan and Endoscopic Ultrasound, and surgery is offered when a lesion is confirmed. In 2015, two patients with a screen-detected solid lesion were identified. In both patients, lesions were visible on MRI and CT scan, while the EUS was unremarkable. Surgical resection of the head of the pancreas resulted in nearly fatal complications in the first patient. This patient was shown to have a benign lesion. In contrast, timely identification of an early cancer in the second patient was accompanied by an uneventful postoperative course. These cases underline the risks inherent to a PDAC prevention program. All patients should be fully informed about the possible outcomes before joining a surveillance program.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the most aggressive forms of cancer. With PDAC currently ranking fourth in terms of cancer-related deaths in the United States (1), the prognosis will only improve if the tumour can be detected and treated at an earlier stage.

Approximately 3–5 % of all patients with PDAC have a genetic predisposition that results in an increased risk of developing the tumor (2) and a substantial proportion of these patients carry an underlying gene defect in CDKN2A/ p16-Leiden (Familial Atypical Multiple Mole Melanoma, FAMMM syndrome), STK11 (Peutz-Jeghers syndrome), the BRCA1/2 genes (Hereditary breast cancer) or one of the MMR genes (Lynch syndrome) (3).

Because surveillance might improve the prognosis in asymptomatic, high-risk individuals, in 2000 a surveillance program for CDKN2A/p16-Leiden mutation carriers was initiated at the department of Gastroenterology and Radiology at the Leiden University Medical Centre (LUMC). Surveillance consists of a yearly MRI, with an option for EUS between two MRI scans. In cases where a pancreatic lesion is suspected, an EUS and CT scan is performed in order to confirm the presence of the lesion. If the lesion is confirmed, pancreatic surgery is offered. In this report, we describe surveillance and treatment results for two CDKN2A/p16-Leiden patients with a screen-detected lesion.

Case 1

The first patient, a 55-year-old male with a CDKN2A/p16-Leiden mutation, was referred to the Department of Gastroenterology and Hepatology at the Leiden University Medical Centre in 2011 to discuss the option of pancreatic surveillance. The patient had no known family history of PDAC, and quit smoking in 2003.

The advantages and disadvantages of the surveillance program were discussed with the patient before he gave informed consent. In the summer of 2015, a solid 8 mm lesion in the uncinate process of the pancreas was detected by MRI (Fig. 1, upper panel). Retrospectively, a small lesion was already visible on the previous MRI in 2014. The patient did not report any complaints and all blood tests were normal, including CA19.9. Subsequent CT scanning confirmed the presence of a solid 10 mm lesion (Fig. 1, lower panel), whereas EUS was normal.

The patient was discussed by a multidisciplinary team and resection was recommended because two of the three imaging tools showed the presence of a solid lesion. During surgical exploration, a small lesion was palpated in the uncinate process of the pancreas and a pylorus-preserving pancreaticoduodenectomy (PPPD) was performed. Pathological examination of the surgical specimen showed a 3 mm small area with sclerotic stroma and inflammation. Amidst the sclerosis ductular proliferation, with focal cribriform architecture was found. SMAD4 and p53 immunostaining was normal. Taking everything into account it was concluded that there was no evidence of (pre)cancer. A total of 23 lymph nodes were identified, all of which were free of tumor.

One day after surgery the patient developed symptoms suggesting leakage of the choledochojenunostomy. During re-exploration the anastomosis was revised. Eight days after the initial surgery, leakage of the pancreatico-jejunostomy led to a re-laparotomy, with revision of the anastomosis with surgical drains left in situ. Nine days after this intervention, the patient's condition deteriorated. Evidence for a new leakage of the pancreatic anastomosis led to a completion pancreatectomy. Eighteen weeks later, a retroperitoneal debridement of necrosis in the former pancreatic bed was performed. Finally, the patient developed a thoracic empyema and a subphrenic abscess treated by thoracotomy and decortication. Following the last intervention the patient recovered slowly and he was discharged in a relatively good physical condition, 5 months after the initial surgery. His diabetes is currently managed with four daily doses of insulin.

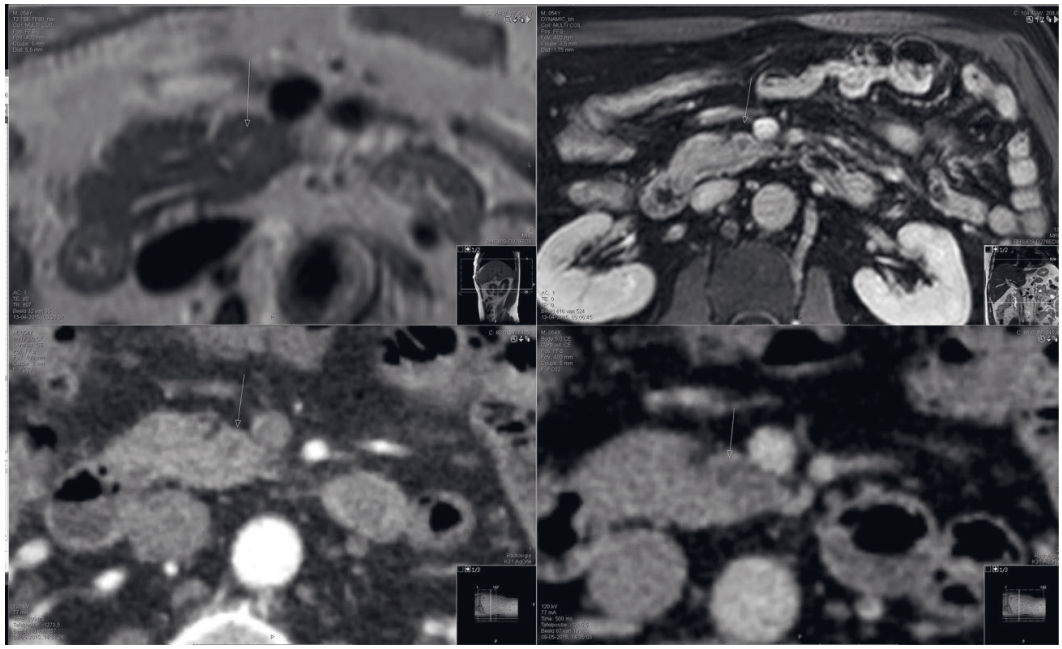

Fig. 1 MRI (upper panel) and CT-scan (lower panel) of the pancreas in case 1

Case 2

The second patient, a 50-year-old male with a CDKN2A/ p16-Leiden mutation, was referred to the department of Gastroenterology and Hepatology. He underwent treatment for melanoma at the ages of 36 and 40. He was asymptomatic and he had never smoked. His father died of PDAC at age 52. After discussion on the benefits and drawbacks, the patient decided to participate in the surveillance program (2012). An MRI scan in November 2015 showed a possible 17 mm lesion with oedema in the head of the pancreas (Fig. 2, upper panel). Retrospectively, a smaller edematous area was present at this site on the previous MRI scan. CT scanning confirmed the presence of a solid 10 mm lesion in the same area (Fig. 2, lower panel), while the EUS was unremarkable. Blood tests did not show any abnormalities. The findings were discussed by the Leiden multidisciplinary team and a PPPD was offered. Following surgery, pathological examination of the surgical specimen showed a 9 mm moderately differentiated PDAC, surrounded by inflammation. The resection margins were free (closed margin 0.3 mm facing the SMV) although there was growth into the peripancreatic tissue. All 15 detected lymph nodes were free of cancer. The patient recovered well after surgery and did not encounter any complications. He was discharged from hospital, in good physical condition, 8 days after initial surgery.

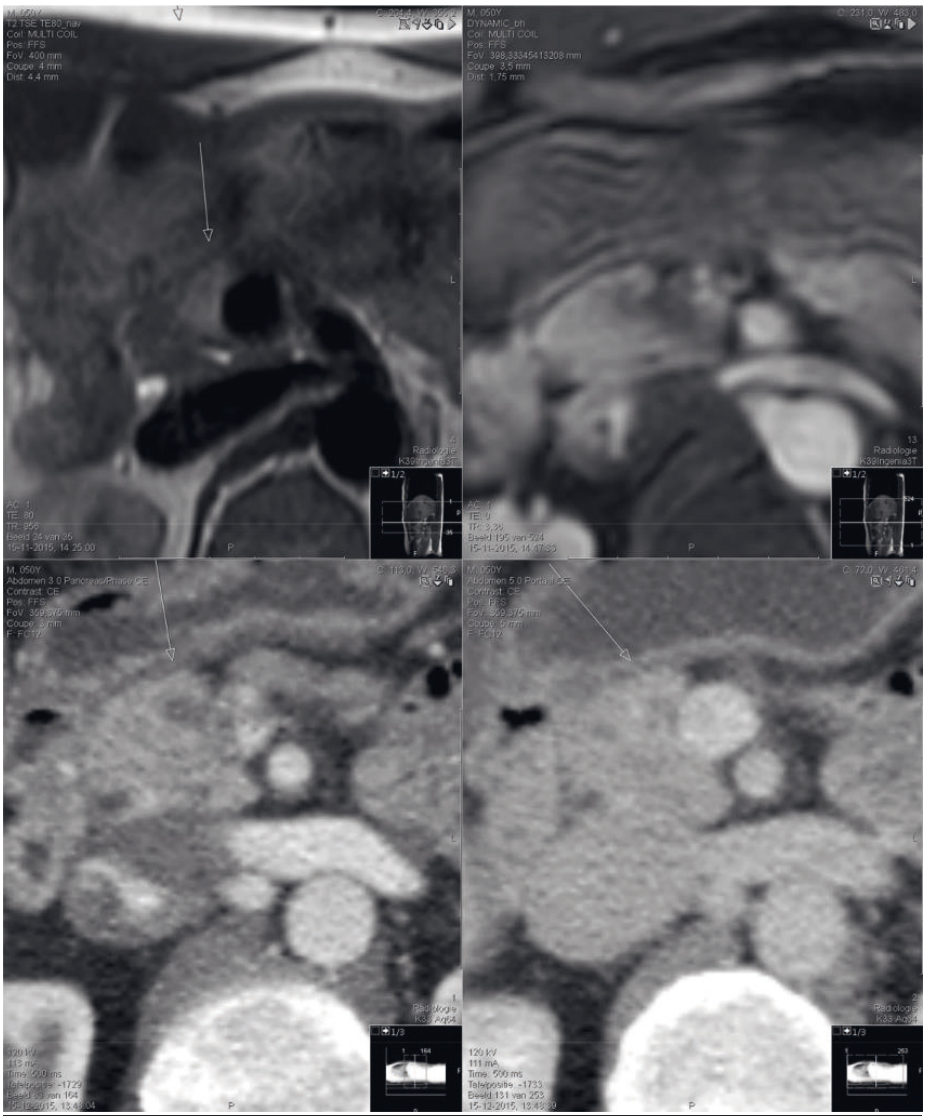

Fig. 2 MRI (upper panel) and CT-scan (lower panel) of the pancreas in case 2

Discussion

These two cases clearly illustrate the dilemmas faced in the surveillance of individuals at high-risk for PDAC. The first patient experienced nearly fatal complications due to surgery and was found to have a benign lesion. This is an example of a worst-case scenario that may occur in this type of surveillance program. The second patient, diagnosed shortly after the

first case, had very similar imaging findings, an uneventful course after surgery, and was eventually shown to have an early cancer.

Several questions arise regarding these two patients:

(a) Did the findings, especially in the first patient, justify surgery? (b) Could the benign nature of the lesion in the first patient have been predicted? (c) How can the surveillance programs be improved? (d) How can a devastating course, as seen in the first patient, be prevented? Regarding the first question, the two imaging techniques (MRI and EUS) reportedly show a high sensitivity and specificity (4), with MRI usually regarded as the best tool to identify cystic lesions and EUS as the best technique for the identification of solid lesions (5). In both cases reported here the presence of a solid lesion was shown on MRI and CT, whereas the EUS was unremarkable. The fact that the lesion was palpated in both patients during surgical exploration confirmed the imaging findings and justified surgery in view of the high risk of PDAC. Lesion growth is a strong indicator for malignancy, but both patients showed only slight lesional growth. Due to the rapid growth of PDAC, another argument in favour of surgery is the short window of time between the detection of a lesion and development of metastatic disease (6). In relation to the second issue, prediction of the benign nature of a lesion, differentiation of benign and malignant lesions by FNA biopsy might have been considered. In this particular case no abnormalities were found on EUS, ruling out EUS-guided biopsy. In retrospect, even if the lesion had been visible on EUS, performance of an FNA biopsy would not have been useful in decision-making in this case because a negative FNA result does not exclude the presence of PDAC.

The second patient was diagnosed shortly after discharge of the first patient. In view of the devastating course in the first patient combined with the identification of a benign lesion, we were very hesitant to offer surgery again. However, based on the same arguments and after consultation with international experts, surgery was offered. The pathological findings following surgery in this case subsequently confirmed that this was the right decision and suggested that postponement of surgery would have impaired the patient's outcome.

Regarding the third question—improvement of surveillance methods—this case report underlines the urgent need for modification of screening methods, especially regarding improvements in the sensitivity of MRI imaging of the pancreas. Additional screening tools should also be developed. At present, the value of the FDG-PET scan in the detection of PDAC is questionable, because the minimum size of lesions detectable by this technique is about 10 mm. However, developments in PET tracers that target specific tumor biomarkers that occur as a consequence of the CDKN2A/p16-Leiden defect could potentially lead to earlier detection (7).

Another way to improve the surveillance program is the use of circulating tumour markers. Slater et al. (8, 9) reported promising results on the use of tumour markers, including micro-RNAs 196a and b, LCN2, and TIMP1. In a small pilot study, the application of proteomics allowed us to differentiate between malignant and benign lesions (10). However, these findings should be confirmed in larger studies.

The final question concerns how the risks of serious complications due to surgery can be minimized. Recent studies suggest that mortality rates for pancreaticoduodenectomies procedure lie somewhere between 0.5 and 6 %, with a morbidity rate of up to 40 % (11, 12). A recent decision model study showed that the possible benefits of a surveillance program may be lost if the mortality rate is slightly increased (13).
The only way to achieve the lowest possible mortality and morbidity rates is to restrict prevention programs to expert centres that carry out larges volume of pancreatic surgeries. Moreover, it is very important to discuss the advantages and disadvantages with a patient prior to their participation in a surveillance program so that the patient is fully aware of the risks. Advantages of the program in CDKN2A/p16-Leiden mutation carriers are that more tumours are identified at a resectable stage (75 % vs. 15–20 % in symptomatic patients) and that the prognosis of patients with screen-detected tumours is better (5-year survival is 24 %) than that of symptomatic patients (5–7 %) (14).
Disadvantages include, (1) the surveillance program cannot guarantee that PDAC is always detected at an early and curable stage, (2) the screening protocol is burdensome and may cause anxiety before and shortly after the screening procedure, (3) there may be false positive and false negative cases, and finally, (4) treatment consists of major surgery, a pancreaticoduodenectomy or distal pancreatectomy depending on the site of the tumor, all of which are associated with substantial morbidity and mortality.

These case reports illustrate the difficult decisions that have to be made in high-risk individuals with a suspected lesion in the pancreas. All involved physicians, together with the patient, should be aware of all possible outcomes of the intervention.

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CHAPTER 8

Summary and Discussion

The benefit of surveillance of the pancreas for the early detection of PDAC

Surveillance of groups at high risk for PDAC may lead to early detection of PDAC or detection of precursor lesions (PRLs), allowing curative surgical treatment. However, before undertaking surveillance on a global scale, we need to first establish whether the surveillance program meets the screening criteria set out by Wilson and Jungner (27). Surveillance of individuals at high risk for PDAC complies with most of these requirements. The target group (ie, individuals with a substantial risk of PDAC [>5 %]) is well defined. Although the natural history of the disease is not completely known, studies have reported that patients with FPC as well as carriers of a CDKN2A mutation frequently develop PRLs including pancreatic intraepithelial neoplasms (PanINs) and intraductal papillary mucinous neoplasms (IPMNs)(7). Surveillance tools (magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography [MRCP], and endoscopic ultrasound [EUS]) that are able to detect small PRLs or early cancers are available(12-14, 17, 28). The surveillance program does not seem to be burdensome for the patients(29). However, it is not yet known whether the surveillance program meets the most important criteria, which are the early detection of cancer or PRLs and an improved prognosis. Previous studies reported data on the yields of surveillance but did not address the benefit of programs in terms of survival(12-14, 17, 28, 30, 31).

In Chapter 2, we described the long-term outcome of prospective surveillance of a large series of CDKN2A/p16-Leiden mutation carriers, BRCA1/2 and PALB2 mutation carriers, and individuals at risk (IARs) for FPC conducted at three expert centers in Marburg, Germany; Leiden, the Netherlands; and Madrid, Spain. The study demonstrated that the resection rate of screendetected PDAC in CDKN2A/p16-Leiden mutation carriers (75%) was much higher than reported for sporadic PDAC patients (15% to 20%) and for historical controls of CDKN2A/p16-Leiden mutation carriers with symptomatic PDAC (15%). The 5-year survival rate was substantially higher (24%) than the survival rate reported for patients with symptomatic sporadic PDAC (4% to 7%).
PRLs were much more frequent in patients with FPC than in CDKN2A/p16-Leiden mutation carriers. Surgical resection was performed in 13 FPC patients (6.1%) with a suspected precursor lesion. Only four lesions (1.9% of all screened patients) were high-risk lesions (grade 3 PanIN or high-grade gastric-type IPMN) and another four IARs showed multifocal grade 2 PanIN lesions in combination with low-grade gastric-type BD-IPMNs and/or atypical flat lesions. The relevance of the latter lesions are still unknown.
Without a control group, it is difficult to determine with certainty the effects of the surveillance program on PDAC outcome. However, in view of the high resection rate and the better survival compared with the survival rates reported for patients with sporadic PDAC, surveillance of CDKN2A/p16-Leiden carriers appears to be beneficial. Whether surveillance of FPC families is effective and improves the prognoses is still questionable. The yield of PDAC is low, and most screen-detected PDACs reported in the literature were advanced cancers(4). Likewise, the yield in terms of detection of relevant PRLs (grade 3 PanIN and high-grade IPMN) was low (1.9%). However, if surgical removal of multifocal grade 2 PanIN and multifocal BD-IPMNs is regarded as beneficial, the diagnostic yield increases to 3.7% (eight of 214 patients), and surveillance of FPC might also be considered effective. In summary, surveillance of CDNK2A mutation carriers was relatively successful, detecting most PDACs at a resectable stage. The value of surveillance of FPC is still not clear, and the main effect seems to be prevention of PDAC by removal of PRLs.

The role of precursor lesions in the development of PDAC in carriers of a P16-Leiden mutation

Recently, we reported a lower frequency of cystic precursor lesions in CDKN2A-p16-Leiden mutation carriers compared with patients from families with familial pancreatic cancer (7). This observation suggests that the process of carcinogenesis in CDKN2A-p16-Leiden mutation carriers might be different from that in FPC. To further understand this issue, we needed to determine whether cystic precursor lesions increase in size over time and develop into PDAC. If cystic lesions indeed play a role in carcinogenesis in this high-risk group, surveillance would be better targeted to patients with cystic precursor lesions.

Finally, information on the growth rate of PDAC might be helpful in decision making regarding appropriate screening intervals.

In the study described in chapter 3, we evaluated (1) the role of precursor lesions in the development of PDAC in CDKN2A-p16-Leiden mutation carriers and assessed (2) the size of screen-detected PDAC in relation to the screening interval.

Cystic lesions were found in a quarter of all mutation carriers. Although most cystic lesions remained stable over time, 3 of 6 patients with at least 1 cystic lesion between 10 and 20 mm developed PDAC. Considering the entire group of mutation carriers, 5 patients with a cystic lesion (9.6%) developed PDAC and a similar proportion (7.0%) developed PDAC in the absence of cysts. The median size of all incident PDAC detected between 9 and 12 months since the previous normal MRI was 15 mm, suggesting an annual growth rate of about 15 mm/year.

What are the explanations for our findings? In previous studies, we reported that cystic precursor lesions were less common in carriers of a CDKN2A-p16-Leiden mutation compared with individuals with FPC (7, 18). In contrast, the risk of PDAC was much higher in CDKN2A-p16-Leiden mutation carriers compared with FPC individuals. These findings suggest that cystic precursor lesions play a minor role in the development of PDAC in CDKN2A-p16-Leiden mutation carriers. The similar risk of PDAC observed in patients with and without cystic precursor lesions in the current study is in agreement with this hypothesis. The development from PanIN grade 1 into PanIN grades 2 and 3, and ultimately PDAC is characterized by accumulation of mutations in genes associated with the development of PDAC including alterations of K-RAS, CDKN2A/P16, TP53, and DPC4 genes. Because the patients in our cohort have already such a (germline) mutation at birth, carcinogenesis and development of PDAC may be accelerated. Such accelerated development of PDAC arising from early (invisible) PanIN lesions may explain the similar risk of PDAC observed in the current study in patients with and without cystic precursor lesions. It may also explain the early age of diagnosis of screendetected PDAC (56 years vs. 66 years reported for sporadic PDAC) and the high growth rate. More studies are needed to confirm this hypothesis.

What are the consequences of our findings for clinical practice? In average risk subjects with cystic lesions suspected for BD-IPMNs, resection is considered if the patient has symptoms attributable to the cyst(s), if the cysts are >3 cm in size, or if the cysts contain mural nodules(10). At the meeting of the International Cancer of the Pancreas Screening Consortium (5), there was no consensus on the size criterion for resection of cystic lesions in high-risk individuals, but the majority agreed that surgery should be considered for suspected BD-IPMNs which were >2 cm. Although larger studies are needed to confirm our findings, a more aggressive approach in this specific group of mutation carriers appears to be justified by our results. In patients with a CDKN2A-p16-Leiden mutation with cystic lesions between

10 and 20 mm, the screening interval might be shortened to 6 to 9 months or additional EUS might be performed. If cystic lesions show worrisome features, surgery is recommended. In view of the substantial size of PDACs detected at 1-year intervals, shorter screening intervals might be recommended for all patients, if further studies show this approach to be cost-effective.

The risk of multiple PDAC in carriers of a P16-Leiden mutation

One of the main features of hereditary cancer is the high risk of developing multiple (synchronous or metachronous) cancer. However, multiplicity might be masked in hereditary PDAC because most patients die within 6–12 months(18).
In chapter 4, we describe two CDKN2A-p16-Leiden patients with multiple PDAC, one with a synchronous and one with a metachronous PDAC. In a previous study, we reported two patients with a CDKN2A-p16- Leiden mutation with metachronous PDAC (32, 33). The studies indicate that multiple PDACs can be found in a substantial proportion, i.e., up to 11%, of CDKN2A-p16- Leiden mutation carriers. However, owing to the current surveillance program for CDKN2A-p16-Leiden carriers, an increasing number of patients with PDAC are diagnosed at an early stage, resulting in a longer life expectancy (18). As a consequence, we expect to diagnose more patients with multiple tumors.

Our findings have immediate clinical implications. Firstly, after detection of a primary PDAC, it is very important to exclude the presence of a second synchronous tumor. As the identification of a second synchronous tumor in patients with sporadic PDAC is very unusual, a second tumor can be easily overlooked, as illustrated by one of the patients presented in this report. Secondly, in patients with hereditary PDAC undergoing partial resection of a primary tumor, close surveillance (e.g., at six month intervals) of the remaining pancreas is of utmost importance, as three of our patients developed a second PDAC (32, 33). The most challenging question is whether we should now offer total pancreatectomy to all CDKN2A-p16-Leiden mutation carriers with primary PDAC. In patients with PDAC with poor prognostic indicators, a partial pancreatectomy is probably still the best option because expected survival is usually less than 2 years and a total pancreatectomy would substantially reduce the remaining quality of life. However, patients with a small lesion (<15 mm) and no evidence of lymph node metastases have a much better prognosis, and total pancreatectomy could be considered. A well-known disadvantage of the total pancreatectomy is the development of diabetes and the associated significant impairment of general quality of life (34). On the other hand, a disadvantage of a partial resection is that, even with intensive surveillance, the chance of detecting a second tumor at an early stage is limited. For CDKN2A-p16 mutation carriers, a total pancreatectomy may therefore bring relief from the ongoing stress associated with the possibility of a second PDAC. We suggest that all the pros and cons of total pancreatectomy are discussed with a patient prior to surgery, resulting in a shared decision.

The cost-effectiveness of surveillance for PDAC in P16-Leiden mutation carriers

During the last two decades, surveillance programs for individuals with an increased risk of PDAC have been implemented in many centers worldwide. A systematic review published in

2015 showed that these programs resulted in higher curative resection rates (60% vs. 25%), longer median survival, and higher 3-year survival rates (35, 36).

Relatively few studies have investigated the cost-effectiveness of surveillance programs for individuals at increased risk of pancreatic cancer. The available studies concluded that pancreatic cancer screening is generally cost-effective in various high-risk groups (37-40). However, no study to date has addressed the cost-effectiveness of screening *CDKN2A*-p16-*Leiden*-mutation carriers. In chapter 5, we evaluated the costs of a surveillance program in a large cohort of *CDKN2A*-p16-*Leiden*-mutation carriers. The specific aims of this study were (1) to assess the resection rate and related survival, and (2) to assess cost-effectiveness.

The study demonstrated that out of the 347 mutation carriers, 31 individuals (8,9 %) developed PDAC and the tumor was resectable in 22 cases (71%). The long-term survival rate for patients with resectable PDAC was estimated at 47,1%,. Cost-effectiveness of annual surveillance was estimated at 14,000 euro per QALY.

To date, four studies have addressed the cost-effectiveness of surveillance for individuals at risk for PDAC. Although all reports showed that PDAC surveillance was cost-effective, the populations analyzed (FPC, carriers of various mutations associated with PDAC development), the screening strategies (once in a lifetime, annual or bi-annual screening) and screening methods (EUS or MRI/MRCP) varied widely between the studies.

In the current study, the cost-effectiveness of annual surveillance was estimated at 14,000 euro per QALY, an estimate that is likely to be acceptable in most countries. We observed that several variables in particular influenced our study results. One important factor was the elevated genetic risk of our patient cohort, as *CDKN2A*-p16-*Leiden*-mutation carriers show a model-estimated lifetime PDAC risk of 37.6%. We estimated that surveillance could be cost-effective for populations with a lifetime risk of at least 10%. This figure matches earlier studies using hypothetical simulation models which suggested that pancreas screening is ineffective in the general population but effective in patients with a substantial risk (41-43). Screening of low-risk individuals was associated with a reduced life expectancy, an outcome attributed to the increased discovery of insignificant lesions and subsequent unnecessary surgical intervention. As an international consortium of experts currently recommends pancreatic surveillance for HRIs with an estimated lifetime risk of PDAC of >5% (5), more studies are needed to assess the cost-effectiveness of surveillance of individuals with a relatively low risk (i.e., <10%).

The other key factor in cost-effectiveness was the ability of the surveillance program to detect PDAC at an earlier stage, which resulted in a considerable increase in patients with resectable PDAC (from 15% to 77.3%). Moreover, a substantial proportion (47,1%, $p<0.001$) of these patients can be cured. Without this observed cure, it would be difficult to exclude the possibility that improved survival due to surveillance was simply due to lead time bias (whereby improved survival after diagnosis is due to earlier diagnosis rather than longer survival). Under the current surveillance program an estimated 33,5% of diagnosed patients are considered cured, which is enough for the program to be cost-effective. Nevertheless, a few patients developed an advanced cancer within the recommended annual surveillance interval of the current program. Shorter intervals might therefore be considered in individuals with additional risk factors for development of PDAC (e.g., smoking, strong family history for PDAC). The sensitivity analysis indicated that bi-annual surveillance could be cost-effective, if it further improved the probability of cure after surgery.

In conclusion, this study demonstrated that screening for PDAC is cost-effective for *CDKN2A*-p16-*Leiden*-mutation carriers. In most patients a screen-detected PDAC could be resected and these patients subsequently benefitted from considerably improved survival.

Incidental findings detected during surveillance for PDAC in familial PDAC and in P16-Leiden mutation carriers

The widespread use of magnetic resonance imaging (MRI) and computed tomography (CT) has led to a substantial increase in the detection of incidental findings, more commonly referred to as incidentalomas. Currently, an increasing number of centers offer surveillance of the pancreas to individuals at high risk (IARs) of pancreatic ductal adenocarcinoma (PDAC), usually involving MRI and/or endoscopic ultrasonography (EUS)(18, 25, 44, 45). Detection of extrapancreatic incidental lesions in these high-risk groups may offer benefit if the lesion is (pre)malignant. However, if only benign lesions are found, additional imaging and surgical intervention might be a burden, especially in high-risk groups that already undergo surveillance for multiple cancers.

In chapter 6, we evaluated the frequency of extrapancreatic incidentalomas in large, long-term, prospective surveillance programs for PDAC at three European expert centers and assessed the benefit of detecting these lesions. The study shows that MRI-based pancreas surveillance programs for PDAC result in the detection of a large number of incidental lesions. The most commonly found lesions were liver cysts, renal cysts and liver hemangioma, which together accounted for 74% of all incidental lesions, followed by adrenal incidentaloma in 6% of patients. Only five (0.9%) patients underwent surgery for a benign lesion: two patients for a liver cyst, one for a renal cyst and two for an adrenal incidentaloma.
Extra-pancreatic cancer was detected in 11 patients (1.9%), including seven CDKN2A-p16-Leiden mutation carriers, and metastatic disease was detected in six of the 11 patients. Early detection of tumors was beneficial in at least five of the patients.
Our findings for benign lesions are in agreement with studies that have reported frequencies of incidental findings detected during abdominal imaging. However, the rate of incidentally detected cancers in the subgroup of CDKN2A-p16-Leiden mutation carriers was much higher. What was the benefit of the detection of incidental lesions in our study? Although incidental findings were frequent, only 0.9% of the total group of IARs underwent a surgical intervention for a lesion, which was then found to be benign in all cases. A primary cancer, metastases of a previous cancer or a new cancer was detected in 1.9% of the total group. By contrast, in the Leiden cohort of CDKN2Ap16- Leiden mutation carriers, extrapancreatic cancer was detected in a substantial proportion of patients (seven patients out of 217 (3.2%)). The early detection of cancers in seven mutation carriers allowed curative resection of renal cancers in two patients, a gastric stromal tumor in one patient and colonic resection (and early start of chemotherapy) in one patient with CRC. In the German cohort, the detection of a renal cell carcinoma allowed curative resection. In addition, the identification of metastatic breast cancer in two patients allowed the early start of chemotherapy.
What are the clinical implications of our findings? First, it is important to inform all participants at the start of the surveillance program about the possibility of detecting usually harmless incidental lesions. However, carriers of a CDKN2A-p16-Leiden mutation should be told that cancer might be detected outside the pancreas in a small

proportion of patients. To improve the investigation of the pancreas, there is currently a trend toward restricting MRI scanning to the pancreas only. However, to avoid missing cancers located outside the pancreas in CDKN2A-p16-Leiden mutation carriers, MRI assessment should include at least one scan of all abdominal organs.

Dilemma's in the management of carriers of a P16-Leiden mutation (chapter 7)

In chapter 7, we describe surveillance and treatment results for two CDKN2A/p16-Leiden patients with a screendetected lesion. These two cases clearly illustrate the dilemmas faced in the surveillance of individuals at high-risk for PDAC. The first patient experienced nearly fatal complications due to surgery and was found to have a benign lesion. This is an example of a worst-case scenario that may occur in this type of surveillance program. The second patient, diagnosed shortly after the first case, had very similar imaging findings, an uneventful course after surgery, and was eventually shown to have an early cancer. In chapter 7, we addressed the following questions regarding these two patients: (a) Did the findings, especially in the first patient, justify surgery? (b) Could the benign nature of the lesion in the first patient have been predicted? (c) How can the surveillance programs be improved?
(d) How can a devastating course, as seen in the first patient, be prevented?

Regarding the first question, the two imaging techniques (MRI and EUS) reportedly show a high sensitivity and specificity (13). In both cases reported here the presence of a solid lesion was shown on MRI and CT, whereas the EUS was unremarkable. The fact that the lesion was palpated in both patients during surgical exploration confirmed the imaging findings and justified surgery in view of the high risk of PDAC. Lesion growth is a strong indicator for malignancy, but both patients showed only slight lesional growth. Due to the reported rapid growth of PDAC, another argument in favour of surgery is the short window of time between the detection of a lesion and development of metastatic disease (25).

In relation to the second issue, prediction of the benign nature of a lesion, differentiation of benign and malignant lesions by FNA biopsy might have been considered. In this particular case no abnormalities were found on EUS, ruling out EUS-guided biopsy. In retrospect, even if the lesion had been visible on EUS, performance of an FNA biopsy would not have been useful in decision-making in this case because a negative FNA result does not exclude the presence
of PDAC.

Regarding the third question—improvement of surveillance methods—this case report underlines the urgent need for modification of screening methods, especially regarding improvements in the sensitivity of MRI imaging of the pancreas. Additional screening tools should also be developed. Another way to improve the surveillance program is the use of circulating tumour markers.

The final question concerns how the risks of serious complications due to surgery can be minimized. Recent studies suggest that mortality rates for pancreaticoduodenectomies procedure lie somewhere between 0.5 and 6 %, with a morbidity rate of up to 40 % (46, 47).

The only way to achieve the lowest possible mortality and morbidity rates is to restrict prevention programs to expert centres that carry out larges volume of pancreatic surgeries.

These case reports illustrate the difficult decisions that have to be made in high-risk individuals with a suspected lesion in the pancreas. It is very important to discuss the advantages and disadvantages with a patient prior to their participation in a surveillance program so that the patient is fully aware of the risks. Advantages of the program in CDKN2A/p16-Leiden mutation carriers are that more tumours are identified at a resectable stage and that the prognosis of patients with screen-detected tumours is better (5-year survival is 24 %) than that of symptomatic patients (5–7 %) (18).
Disadvantages include, (1) the surveillance program cannot guarantee that PDAC is always detected at an early and curable stage, (2) the screening protocol is burdensome and may cause anxiety before and shortly after the screening procedure, (3) there may be false positive and false negative cases, and finally, (4) treatment consists of major surgery, a pancreaticoduodenectomy or distal pancreatectomy depending on the site of the tumor, all of which are associated with substantial morbidity and mortality.

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CHAPTER 9

Samenvatting en discussie

De waarde van surveillance van de pancreas voor de vroege opsporing van ductaal adenocarcinoom van de pancreas (PDAC)

Surveillance van groepen met een hoog risico op PDAC kan leiden tot vroege detectie van PDAC of precursor lesies (PRL's)(voorloper lesies), waardoor genezing door operatieve verwijdering van de lesie mogelijk wordt. Voordat surveillance op grote schaal toegepast kan worden, moet vastgesteld worden of het surveillanceprogramma voldoet aan de criteria opgesteld door Wilson en Jungner. Surveillance van personen die een hoog risico hebben op PDAC voldoet aan de meeste van deze voorwaarden. De doelgroep (i.e. personen met een aanzienlijk verhoogd risico op PDAC) is goed gedefinieerd. Hoewel het natuurlijk beloop van de ziekte niet volledig bekend is, hebben studies aangetoond dat patiënten met familiair pancreas carcinoom (FPC) en dragers van de CDKN2A mutatie vaak precursor lesies ontwikkelen zoals pancreatische intra-epitheliale neoplasma's (PanIN's) en intraductale papillaire mucineuze neoplasma's (IPMN's). Er zijn ook screening's methoden beschikbaar (MRI, MRCP en EUS), die kleine PRL's en tumoren kunnen detecteren. Het surveillanceprogramma lijkt niet overmatig belastend te zijn voor de patiënten. Maar nog niet bekend is of het screeningsprogramma ook voldoet aan het meest belangrijke criterium, namelijk, de opsporing van precursor laesies of de tumoren in een vroeg stadium en een verbeterde overleving. Eerdere studies publiceerden over de *opbrengst* van surveillance maar niet over het effect van surveillance programma's op de overleving.

In hoofdstuk 2, beschreven we de lange-termijn uitkomsten van een prospectief screeningsonderzoek bij een grote groep van CDKN2A/p16-Leiden mutatie dragers, BRCA1/2 en PALB2 mutatie dragers, en individuen die een verhoogd risico hebben op FPC, uitgevoerd door drie expert centra in Marburg, Duitsland; Leiden, Nederland en Madrid, Spanje. De studie toonde aan dat het resectiepercentage (75%) van PDAC bij gescreende patiënten van CDKN2A mutatie dragers veel hoger was dan beschreven voor sporadische PDAC patiënt groepen (15 tot 20%) en voor historische controles van CDKN2A/p16-Leiden mutatie dragers met symptomatisch PDAC (15%). De 5-jaars overleving was aanzienlijk hoger (24%) in vergelijking met de overleving van patiënten met symptomatische sporadische PDAC (4% tot 7%). PRL's kwamen vaker voor bij patiënten met FPC dan bij CDKN2A mutatie dragers. Dertien FPC patiënten (6.1%) met een verdachte PRL hebben een chirurgische resectie ondergaan. Slechts vier laesies (1.9% van alle gescreende patiënten) waren afwijkingen geassocieerd met een hoog risico op PDAC (graad 3 PanIN of hooggradige gastrisch-type IPMN) en vier andere patiënten hadden multifocaal graad 2 PanIN in combinatie met laaggradig gastric-type side branch-IPMN en/of atypisch vlakke laesies. De relevantie van de laatstgenoemde laesies is nog onbekend.
Zonder een controlegroep is het moeilijk om met zekerheid het effect vast te stellen van het surveillanceprogramma op PDAC. Maar gezien het hoge resectie percentage en de betere overleving in vergelijking met het resectie percentage en de overleving voor patiënten met sporadische PDAC, lijkt screening van CDKN2A/p16-leiden dragers effectief. Of surveillance van FPC-families ook effectief is en de prognose verbetert, is echter de vraag. Het aantal door screening vastgestelde PDAC is laag, en de meeste PDAC's beschreven in de literatuur die gedetecteerd zijn door screening van FPC families waren vergevorderde kankers. De opbrengst ten aanzien van detectie van relevante PRL's (graad 3 PanIN en hooggradige IPMN)

was eveneens laag (1.9%). Maar als chirurgische verwijdering van multifocale graad 2 PanIN en multifocale sidebranch-IPMN's als relevant wordt beschouwd, stijgt de diagnostische opbrengst naar 3.7% (acht van de 214 patiënten), en kan screening van FPC ook als effectief worden beschouwd. Samenvattend was de surveillance van CDKN2A mutatie dragers relatief succesvol, waarbij de meeste PDAC's in een resectabel stadium werden gedetecteerd. De waarde van surveillance voor FPC is nog niet geheel duidelijk en het belangrijkste effect lijkt de preventie van PDAC te zijn door het verwijderen van PRL's.

De rol van precursor lesies bij de ontwikkeling van PDAC bij dragers van de p16-Leiden mutatie

In een recent onderzoek, publiceerden we over een lagere frequentie van cysteuze precursor laesies bij CDKN2A-p16-Leiden mutatie dragers in vergelijking met patiënten uit families met familiair pancreascarcinoom (FPC; ref18). Deze bevindingen suggereren dat het proces van carcinogenese bij CDKN2A-p16-Leiden mutatie dragers mogelijks anders is dan bij FPC. Om dit beter te begrijpen, is het nodig om te onderzoeken of cysteuze precursor lesies in de loop van de tijd toenemen in grootte en zich ontwikkelen tot PDAC. Als cysteuze laesies inderdaad een rol spelen bij de carcinogenese van pancreascarcinoom bij hoog-risico groepen, zou het mogelijk beter zijn om de screening vooral te richten op patiënten met zulke lesies. Tenslotte kan informatie over de groeisnelheid van PDAC nuttig zijn voor het bepalen van het juiste screeningsinterval.

In de studie beschreven in hoofdstuk 3, evalueerden we (1) de rol van precursor laesie bij de ontwikkeling van PDAC bij CDKN2A-p16-Leiden mutatie dragers en onderzochten we (2) de grootte van de door screening vastgestelde PDAC in relatie tot het screenings interval. Cysteuze laesies werden bij een kwart van alle mutatie dragers vastgesteld. Hoewel de meeste cysteuze laesies in de loop van de tijd stabiel bleven qua grootte, ontwikkelden drie van de zes patiënten met ten minste 1 cysteuze laesie tussen de 10 en 20 mm, PDAC. In de gehele groep van mutatiedragers, ontwikkelden 5 van de patiënten met een cysteuze laesie (9.6%) PDAC en een vergelijkbaar percentage (7.0%) ontwikkelde PDAC in de afwezigheid van cysten. De mediane grootte van alle incidente PDAC gedetecteerd tussen de 9 en 12 maanden na de vorige normale MRI was 15mm, hetgeen een jaarlijkse groeisnelheid suggereert van ongeveer 15mm/jaar.

Wat zijn de verklaringen voor onze bevindingen? In eerdere studies beschreven we dat cysteuze precursor laesies minder voorkwamen bij dragers van de CDKN2A-p16-Leiden mutatie in vergelijking met FPC. Daarentegen was het risico op PDAC veel hoger bij CDKN2A-p16-Leiden mutatiedragers in vergelijking met personen met FPC. Deze bevindingen suggereren dat cysteuze precursor laesies een ondergeschikte rol spelen bij de ontwikkeling van PDAC bij CDKN2A-p16-Leiden mutatiedragers. Het vergelijkbare risico van PDAC in de huidige studie bij personen met en zonder cystische precursor laesies komt overeen met deze hypothese. De ontwikkeling van PanIN graad 1 in PanIN graad 2 en 3, en uiteindelijk PDAC wordt gekarakteriseerd door de accumulatie van mutaties in genen geassocieerd met de ontwikkeling van PDAC, zoals K-RAS, CDKN2A/p16, TP53 en DPC4. Omdat de patiënten in onze onderzoeksgroep al een (kiembaan) mutatie bij de geboorte hebben, zou de carcinogenese en ontwikkeling van PDAC versneld kunnen plaatsvinden. Een dergelijke

versnelde ontwikkeling van PDAC ontstaan uit kleine (nog onzichtbare) PanIN laesies zou mogelijk de verklaring kunnen zijn voor het vergelijkbare risico van PDAC geobserveerd in de huidige studie bij patiënten met en zonder cystische precursor laesies. Het kan ook de verklaring zijn voor de vroege leeftijd van diagnose bij screenings gedetecteerde PDAC (56 jaar versus 66 jaar bij sporadische PDAC) en de hoge groeisnelheid. Meer studies zijn nodig om deze hypothese te bevestigen.
Wat zijn de implicaties van onze bevindingen voor de klinische praktijk? Bij personen zonder erfelijke belasting met cysteuze laesies verdacht voor sidebranch IPMNs, wordt resectie overwogen (1) als de patiënt symptomen heeft veroorzaakt door de cyste, (2) als de cyste >3cm in grootte is of (3) als de cyste murale noduli bevat. Bij de bijeenkomst van het Internationaal Pancreaskanker Screening Consortium (2013), was er geen consensus over het beleid ten aanzien van de grootte van een cysteuze lesie als indicatie voor resectie bij hoog risico individuen, maar de meerderheid van de aanwezigen was het erover eens dat in deze gevallen een operatie overwogen moet worden voor sidebranch IPMN's die >2cm waren. Hoewel grotere studies nodig zijn om onze bevindingen te bevestigen, is een meer agressieve benadering bij deze specifieke groep van mutatie dragers gerechtvaardigd. Bij patenten met een CDKN2A-p16-Leiden mutatie met cysteuze laesies tussen 10 en 20mm, kan het screeningsinterval verkort worden naar 6 tot 9 maanden of kan aanvullend een EUS verricht worden. Als cysteuze laesies "worrisome" kenmerken tonen, wordt chirurgie aanbevolen. Gezien de aanzienlijke afmetingen van PDAC's (15 mm) vastgesteld na een interval van een jaar, kunnen kortere screeningsintervallen overwogen worden bij *alle* patiënten, als toekomstige studies laten zien dat dit beleid kosteneffectief is.

Het risico op multipele PDAC bij dragers van een p16-leiden mutatie

Een van de belangrijkste kenmerken van erfelijke kanker is het hoge risico op het ontwikkelen van multipele (synchrone of metachrone) tumoren. Bij erfelijke PDAC, kan het verhoogde risico verhuld worden omdat de meeste patiënten overlijden binnen 6-12 maanden na de diagnose.
In hoofdstuk 4 beschrijven we twee CDKN2A-p16-Leiden patiënten met multipele PDAC, één met een synchrone en één met een metachrone PDAC. In een eerdere studie, beschreven we twee patiënten met een CDKN2A-p16-Leiden mutatie met metachrone PDAC. Het onderzoek toont aan dat bij een substantieel aantal patiënten multiple PDAC's vastgesteld kunnen worden, i.e., tot 11% van de CDKN2A mutatie dragers. Door het huidige surveillanceprogramma voor CDKN2A-p16-Leiden dragers wordt bij een toenemend aantal patiënten, PDAC in een vroeg stadium gediagnosticeerd, wat resulteert in een hogere levensverwachting. Als gevolg hiervan verwachten we in de toekomst bij meer patiënten multiple tumoren te kunnen vaststellen.

Onze bevindingen hebben directe klinische consequenties. Ten eerste is het bij het diagnosticeren van een primaire PDAC erg belangrijk om na te gaan of er een tweede synchrone tumor aanwezig is. Aangezien een tweede synchrone tumor bij patiënten met sporadische PDAC zo weinig voorkomt, kan een tweede tumor makkelijk gemist worden, zoals geïllustreerd door een van de patiënten beschreven in dit artikel. Ten tweede, bij

patiënten met erfelijke PDAC die een partiële pancreasresectie vanwege PDAC hebben ondergaan, is frequent onderzoek (bijvoorbeeld MRI met tussenpozen van zes maanden) van de resterende pancreas heel belangrijk, omdat drie van onze patiënten een tweede PDAC ontwikkeld hebben. Een vraag die zich opdringt is of we een totale pancreatectomie zouden moeten aanbieden aan alle CDKN2A-p16-Leiden mutatie dragers met een primaire PDAC. Bij patiënten met slechte prognostische indicatoren, zou een partiele pancreatectomie de beste optie zijn omdat de verwachte overleving minder dan 2 jaar is en een totale pancreatectomie de resterende kwaliteit van leven aanzienlijk zou verminderen. Maar bij patiënten met een kleine laesie (<15mm) en zonder aanwijzingen voor lymfeklier metastasen en derhalve een veel betere prognose, zou een totale pancreatectomie overwogen kunnen worden. Een nadeel van een totale pancreatectomie is de ontwikkeling van diabetes met daarbij significante vermindering van de kwaliteit van leven. Anderzijds is een nadeel van een partiële resectie dat zelfs bij intensieve surveillance, de kans op het vroegtijdig opsporen van een tweede tumor beperkt is. Daarom kan een totale pancreatectomie voor CDKN2A-p16 mutatie dragers de stress en angst voor de mogelijkheid van ontwikkeling van een tweede PDAC (na een partiële pancreatectomie) doen verminderen. We stellen voor dat alle voordelen en nadelen van een totale pancreatectomie met de patiënt besproken worden vóór de operatie, zodat gezamenlijk een beslissing gemaakt kan worden.

De kosteneffectiviteit van surveillance voor PDAC in P16-Leiden mutatie dragers

De laatste twee decennia zijn wereldwijd in veel centra surveillance programma's geïmplementeerd voor personen met een verhoogd risico op PDAC. Een systematisch review gepubliceerd in 2015, toonde aan dat deze programma's resulteerden in een hoger curatief resectiepercentage (60% versus 25%), langere mediane overleving, en een hogere 3-jaars overleving in vergelijking met symptomatisch PDAC.

Relatief weinig studies hebben de kosteneffectiviteit onderzocht van surveillanceprogramma's voor personen met een verhoogd risico op pancreas carcinoom. De beschikbare studies concluderen dat screening op pancreas carcinoom over het algemeen kosteneffectief is bij verschillende hoog risico groepen. Tot op heden is geen onderzoek verricht naar de kosteneffectiviteit van screening bij CDKN2A-P16-Leiden mutatiedragers. In hoofdstuk 5, evalueerden we de kosten van een surveillanceprogramma in een groot cohort van *CDKN2A*-p16-*Leiden* mutatiedragers. De specifieke doelstellingen van deze studie waren (1) het beoordelen van het resectie percentage en de daarmee samenhangende overleving, en (2) het beoordelen van de kosteneffectiviteit.

De studie toonde aan dat van de 217 mutatiedragers, tweeëntwintig personen (10%) PDAC ontwikkelden en dat de tumor resectabel was in 17 gevallen (77.3%). Het overlevingspercentage op de lange termijn voor patiënten met resectabel PDAC werd geschat op 30.8%, vergeleken met 0% voor patiënten met een irresectabele tumor. De kosteneffectiviteit van jaarlijkse screening werd geschat op 18,000 euro per QALY.

Tot op heden, hebben vier studies de kosteneffectiviteit van screening voor personen met een verhoogd risico op PDAC beschreven. Hoewel alle rapporten aantoonden dat screening

van PDAC kosteneffectief was, varieerden de onderzochte populaties (FPC of dragers van verschillende mutaties geassocieerd met de ontwikkeling van PDAC), de screenings strategieën (een keer in het leven, jaarlijks of tweejaarlijkse screening) en screeningsmethoden (EUS of MRI/MRCP) sterk tussen de studies.

In de huidige studie wordt de kosteneffectiviteit voor jaarlijkse surveillance geschat op 18,000 euro per QALY, een schatting die in de meeste landen waarschijnlijk acceptabel is. We stelden vast dat bepaalde variabelen invloed hadden op de onderzoeksresultaten. Een belangrijke factor was het verhoogde genetische risico van onze patiënten groep, aangezien CDKN2A-p16-Leiden mutatiedragers een door het model geschat levenslang PDAC risico van 37.6% lieten zien. We schatten dat surveillance kosteneffectief kan zijn voor populaties met een levenslang risico van ten minste 10%. Dit cijfer komt overeen met eerdere studies met hypothetische simulatie modellen die suggereerden dat pancreasscreening niet effectief is in de algemene bevolking, maar effectief is bij patiënten met een verhoogd risico. Screening van laag-risico personen is geassocieerd met een verminderde levensverwachting, een uitkomst die verklaard wordt door de toename van het vinden van insignificante laesies welke hebben geleid tot onnodige chirurgische interventie. Aangezien een internationaal consortium van deskundigen momenteel pancreas surveillance adviseert voor hoog-risico individuen met een geschat levenslang risico op PDAC van >5%, zijn meer studies nodig om te bepalen of ook screening voor personen met een relatief laag risico (i.e. <10%) kosten effectief is.

De andere belangrijke factor voor de kosteneffectiviteit was het vermogen van het surveillance programma om PDAC te detecteren in een vroeg stadium, hetgeen in onze onderzoekspopulatie resulteerde in een aanzienlijke toename van patiënten met resectabele PDAC (van 15% tot 77.3%). Bovendien blijkt een aanzienlijke aantal (30.8%, p=0.04) van deze patiënten genezen te kunnen worden. Zonder deze waargenomen genezing, zou het moeilijk zijn om de mogelijkheid uit te sluiten dat de verbeterde overleving als gevolg van screening te wijten was aan de “lead time” bias (waarbij betere overleving na diagnose eerder te wijten is aan eerdere diagnose dan aan langere overleving). In het huidige screeningsprogramma wordt naar schatting 23.8% van de gediagnosticeerde patiënten als genezen beschouwd, wat voldoende is om het screeningsprogramma kosteneffectief te maken. Desondanks ontwikkelden een paar patiënten vergevorderde kanker binnen het aanbevolen jaarlijkse screeningsinterval van het huidige programma. Bij personen met aanvullende risicofactoren voor PDAC (vb. roken, familiegeschiedenis met PDAC) zouden kortere intervallen overwogen kunnen worden. De sensitiviteits analyse gaf aan dat halfjaarlijkse surveillance kosteneffectief kan zijn, als het de kans op genezing na een operatie verder zou verbeteren.

Concluderend heeft deze studie aangetoond dat screening voor PDAC kosteneffectief is voor *CDKN2A*-p16-*Leiden* mutatiedragers. Bij de meeste patiënten kon een door screening gedetecteerde laesie operatief verwijderd worden en deze patiënten hadden vervolgens een aanzienlijk betere overleving.

Incidentele bevindingen gedetecteerd tijdens screening voor PDAC in familiaire PDAC en in P16-Leiden mutatiedragers

Het wijdverspreid gebruik van MRI- en CT-scan heeft geleid tot een aanzienlijke toename in de detectie van incidentele bevindingen, ook wel incidentalomen genoemd. Momenteel is er een toenemend aantal centra die screening van de pancreas aanbieden aan individuen met een verhoogd risico op ductaal adenocarcinoom van de pancreas (PDAC), waarbij meestal MRI en/of echo-endoscopie (EUS) wordt gebruikt. Detectie van extrapancreatische incidentele laesies in deze hoog-risico groepen kan voordelig zijn als de laesie (pre)maligne is. Maar als alleen maar benigne lesies worden gevonden, kunnen aanvullende beeldvorming en chirurgische interventie in hoge mate belastend zijn, vooral bij risicogroepen die al periodiek onderzoek ondergaan voor de vroege opsporing van meerdere kankers.

In hoofdstuk 6 evalueerden we de frequentie van extrapancreatische incidentalomen in grote, langlopende prospectieve surveillanceprogramma's voor PDAC in drie Europese expert centra en onderzochten we het belang van het detecteren van deze laesies. De studie toonde aan dat surveillance programma's voor PDAC met MRI resulteren in de detectie van grote aantallen incidentele laesies. De meest voorkomende laesies waren levercystes, niercystes en leverhemangioom, die samen goed waren voor 74% van alle incidentele laesies, gevolgd door bijnier incidentaloma bij 6% van de patiënten. Slechts vijf (0.9%) patiënten ondergingen een operatie voor een benigne lesie: twee patiënten voor een levercyste, één voor een niercyste en twee voor een bijnier incidentaloom.
Kanker werd gedetecteerd bij 11 patiënten (1.9%), waaronder zeven CDKN2A-p16-Leiden mutatiedragers. Bij zes van de 11 patiënten was er sprake van gemetastaseerde ziekte. Vroege detectie van de tumoren bleek zinvol bij tenminste vijf patiënten.
Onze bevindingen ten aanzien van goedaardige laesies zijn in overeenstemming met studies die frequenties van incidentele bevindingen beschreven bij abdominale beeldvorming. Maar het percentage incidenteel ontdekte kankers in de subgroep van CDKN2A-p16-Leiden mutatiedragers was veel hoger.
Wat was de waarde van de detectie van incidentele laesies in onze studie? Hoewel incidentele bevindingen frequent voorkwamen, onderging slechts 0.9% van de hoog risico individuen (HRIs) een chirurgische interventie voor een laesie, die vervolgens in alle gevallen goedaardig bleek te zijn. Kanker, metastasen hiervan of metastasen van eerdere kanker werd gedetecteerd in 1.9%. Daarentegen werd in het Leidse cohort van CDKN2A-p16-Leiden mutatiedragers extrapancreatische kanker gedetecteerd in een aanzienlijke deel van de patiënten (zeven patiënten van 217 (3.2%)). De vroege detectie van kanker bij zeven mutatiedragers maakte curatieve resectie van nierkanker bij twee patiënten mogelijk, evenals de resectie van een stromale tumor van de maag bij één patiënt en colonresectie (en vroege start van chemotherapie) bij één patiënt met colorectaal carcinoom. In het Duitse cohort maakte detectie van een niercel carcinoom curatieve resectie mogelijk. Bovendien leiden het vaststellen van gemetastaseerde mamacarcinoom bij twee patiënten tot een vroege start van chemotherapie mogelijk.
Wat zijn de klinische implicaties van onze bevindingen? Ten eerste is het belangrijk om alle deelnemers bij de start van het screeningsprogramma te informeren over de mogelijkheid van het opsporen van vaak onschuldige incidentele laesies. Met dragers van een CDKN2A-

p16-Leiden mutatie moet besproken worden dat kanker gedetecteerd kan worden buiten de pancreas in een kleine percentage van de patiënten. Om het onderzoek van de pancreas te verbeteren, is er momenteel een trend om de MRI scan te beperken tot de pancreas. Om te voorkomen dat kankers buiten de pancreas gemist worden bij CDKN2A-p16-Leiden mutatiedragers, zou een MRI beoordeling tenminste één scan moeten bevatten van alle abdominale organen.

Dilemma's bij de behandeling van dragers van een P16-Leiden mutatie

In hoofdstuk 7, beschrijven we de surveillance- en behandelingsresultaten van twee CDKN2A/p16-Leiden patiënten met een door screening gedetecteerde laesie. Deze twee gevallen illustreren duidelijk het dilemma welke zich kan voordoen bij de surveillance van personen met een verhoogd risico op PDAC. De eerste patiënt ontwikkelde bijna fatale complicaties na de operatie en bleek uiteindelijk een benigne laesie te hebben. Dit is een voorbeeld van een "worst-case scenario" waarmee we te maken kunnen hebben bij dit type surveillanceprogramma's. De tweede patiënt werd kort na de eerste patiënt gediagnosticeerd, en had vergelijkbare afwijkingen op de beeldvorming. Het postoperatieve beloop was ongestoord en het pathologische onderzoek toonde een vroeg stadium van kanker aan.

In hoofdstuk 7 gingen we in op de volgende vragen betreffende deze patiënten:
(a) Rechtvaardigden de radiologische bevindingen, met name bij de eerste patiënt, een operatie?
(b) Kon de benigne aard van de laesie bij de eerste patiënt voorspeld worden?
(c) Hoe kan het surveillanceprogramma worden verbeterd?
(d) Hoe kan het kritische beloop, zoals bij de eerste patiënt, voorkomen worden?

Met betrekking tot de eerste vraag, veel onderzoek bevestigen de hoge sensitiviteit en specificiteit van de toegepaste beeldvormende technieken (MRI en EUS). In beide gevallen werd de aanwezigheid van een solide laesie aangetoond op zowel de MRI als de CT-scan, terwijl de EUS geen afwijkingen liet zien. Het feit dat de laesie palpabel was in beide patiënten tijdens de chirurgische exploratie bevestigde de bevindingen van de beeldvorming en rechtvaardigde de chirurgische resectie gezien het hoge risico op PDAC. Eventuele groei van de laesie is een sterke indicator voor maligniteit, maar beide patiënten vertoonden slechts een geringe groei van de afwijking. Vanwege de gerapporteerde snelle groei van PDAC , is een ander argument voor vroegtijdig chirurgisch ingrijpen, het korte tijdsbestek tussen detectie van de laesie en de ontwikkeling van gemetastaseerde ziekte.

Met betrekking tot de tweede vraag (voorspelling van de benigne aard van de laesie bij de eerste patiënt) kan voor de differentiatie tussen benigne en maligne laesies, aanvullende FNA biopsie overwogen worden. Bij onze patiënt werden echter geen afwijkingen gevonden bij EUS, waardoor EUS-geleide biopsie niet mogelijk was. Retrospectief, zou zelfs als de laesie zichtbaar was bij EUS, een FNA-biopsie niet nuttig zijn bij de besluitvorming van deze casus omdat een negatieve FNA (geen carcinoom) de aanwezigheid van PDAC niet uitsluit.

Met betrekking tot de derde vraag – hoe kan het surveillance programma worden verbeterd? – onderstreept dit artikel de noodzaak voor verbetering van screeningsmethoden, met name

van de sensitiviteit van de MRI van de pancreas. Er moeten ook nieuwe screeningsmethoden ontwikkeld worden. Een mogelijke manier om het screeningsprogramma te verbeteren is het gebruik van circulerende tumormarkers.

De laatste vraag betreft, hoe de risico's op ernstige complicaties als gevolg van de operatie geminimaliseerd kunnen worden. Recente studies suggereren dat het sterftecijfer van pancreaticoduodenectomiëen ergens tussen de 0.5 en 6% liggen, met een morbiditeit percentage tot 40%. De enige manier om de laagst mogelijke mortaliteits- en morbiditeit percentages te bereiken, is door de surveillance- programma's en behandeling te beperken tot expertise centra die grote aantallen pancreasoperaties uitvoeren.

De gepresenteerde ziektegevallen illustreren de moeilijke beslissingen die genomen moeten bij hoog-risico individuen met een verdachte afwijking in de pancreas. Het is erg belangrijk om de voor- en nadelen te bespreken met een patiënt voordat zij deelnemen aan een surveillanceprogramma zodat de patiënt zich volledig bewust is van de risico's.

Voordelen van het programma voor CDKN2A/p16-Leiden mutatie dragers zijn dat een groter percentage tumoren geïdentificeerd kan worden in een resectabel stadium en dat hierdoor de prognose voor patiënten met een screenings-gedetecteerde tumor beter is (5-jaarsoverleving is 24%) dan die voor symptomatische patiënten (5-7%).
Nadelen zijn onder meer: (1) het screeningsprogramma kan niet garanderen dat PDAC altijd gedetecteerd wordt in een vroeg en curatief stadium, (2) het screenings protocol is belastend en kan onrust en angst veroorzaken vóór en kort na de screeningsprocedure, (3) er kunnen vals positieve en vals negatieve screeningsuitslagen zijn, en als laatste, (4) de behandeling bestaat uit een grote operatie, afhankelijk van de plaats van de tumor, een pancreaticoduodenectomie of distale pancreatectomie , die gepaard gaat met een aanzienlijke morbiditeit en mortaliteit.

CHAPTER 10

10

Acknowledgement

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***Shared first or last author**

Dankwoord

Professor Hans Vasen. Dankzij uw aanmoedigingen heb ik dit project kunnen voltooien en uw begeleiding heeft bijgedragen aan mijn wetenschappelijke en persoonlijke ontwikkeling.

Professor Hans Morreau, mijn promotor, zonder uw expertise en de talloze pathologische preparaten die u onderzocht heeft, zou dit onderzoek niet mogelijk zijn.

Mijn dank aan co-promotor dr. Martin Wasser. Uw beschikbaarheid en bereidheid om laagdrempelig binnen te lopen voor het beantwoorden van vragen was van grote waarde.

Mijn paranimf Liz Cuperus, bedankt voor je morele en fysieke steun tijdens deze dag. We hebben elkaar ontmoet tijdens de studie en onze vriendschap is gegroeid tijdens onze werkperiode in het HMC. Je bent niet alleen een goede en slimme dokter (en nu mede PhD'er), maar de positiviteit waarmee jij in het leven staat is iets waar ik nog steeds van leer en probeer toe te passen op mijn eigen leven. Bedankt voor alle leuke avonden, de lekkere etentjes en de goede gesprekken.

Lieve mama en papa, bedankt voor jullie onvoorwaardelijke liefde en al het begrip en de steun op de momenten dat ik het zwaar had. Alle opofferingen die jullie hebben gemaakt hebben ervoor gezorgd dat ik nu hier kan staan. Jullie hebben mij geleerd om door te zetten wat er ook op mijn pad komt. Bedankt voor alle maaltijden en pakketjes zodat ik me volledig op mijn studie en PhD kon richten, bedankt voor al het brengen en ophalen op welk moment dan ook, bedankt voor alle hulp bij de verhuizingen doordat ik weer in een ander stad ging studeren.

Lieve Ishara, mijn kleine zusje, toen ik hieraan begon was jij nog niet eens begonnen met studeren. Maar ook jij hebt laten zien dat je een enorm doorzettingsvermogen hebt. Toen je begon met studeren moest ik jou helpen met je wetenschappelijke opdrachten en nu vraag ik jouw hulp om mijn artikelen na te kijken of mij te helpen met het uitvoeren van een analyse. Ik ben enorm trots op wat je allemaal hebt bereikt en hoe je bent gegroeid, bedankt dat je mijn paranimf bent.

En als laatste maar zeker niet de minste Ali Sadeghi, mijn man en beste vriend. Bedankt voor het begrip en de steun als ik weer veel te druk was met werk en/of mijn PhD. Bedankt dat je mij altijd aan het lachen maakt en een goed gevoel geeft. Thuiskomen naar jou is het allerbeste wat me is overkomen.

Curriculum Vitae

Isaura Ibrahim was born on October 13th, 1989 in Utrecht, The Netherlands. Her interest in Oncology was already sparked during elementary school, because of a book she read. At that time she decided she wanted to become a doctor.

After graduating from the Atheneum at Theresialyceum in Tilburg in 2009, she studied Biomedical Sciences in Antwerp and Amsterdam for two years before starting Medical School at Leiden University.

During her third year of Medicine she completed an internship at the Gastroenterology Department, where she met Prof. Dr. HFA Vasen. They co-wrote her first report on the *CDKN2A/p16-Leiden* study population, which was accepted in het Journal of Clinical Oncology. Following this, she began her PhD trajectory alongside her Medical Internships.

During the internship breaks, she participated in international collaboratives at University Clinic Gieβen and Marburg, Germany, to learn more about Biomarker Studies and at Massachusetts General Hospital, USA to learn about computerized cost-effective analysis. During her final year of Medical studies, she was accepted into a residency training program in Gastroenterology and Hepatology and is currently working at the Leiden University Medical Center (program director dr. A. Langers). Isaura lives in the Hague, together with her husband Ali Sadeghi.