Familial Melanoma and Pancreatic Cancer: studies on genotype, phenotype and surveillance

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Limited resection of pancreatic cancer in high-risk patients can result in a second primary

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SUMMARY

Up to 10% of patients with pancreatic ductal adenocarcinoma (PDAC) have either a positive family history for pancreatic cancer (Familial Pancreatic Cancer), or an underlying germline mutation in specific genes (e.g. *CDKN2A*, *BRCA2*) associated with hereditary tumour syndromes. Guidelines have recently been established for the surveillance and management of individuals with a high risk for PDAC, but no recommendations were provided regarding the extent of surgery, that is partial or total pancreatectomy, in cases with a small screen-detected PDAC. This is an important issue because it seems very likely that a hereditary background increases the risk for a second primary cancer of the pancreas. Here we describe two high-risk individuals who developed a second primary cancer after a partial pancreatectomy of an early-stage cancer. Based on these cases, we discuss the pros and cons of total pancreatectomy in high-risk individuals with an early-stage PDAC.

BACKGROUND

Despite medical progress and improved diagnostic and surgical procedures, pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal cancers and is currently the fourth leading cause of cancer-related death in the western world. Only a minority of patients are diagnosed at an early stage of the disease.[1] Pancreatic surveillance of asymptomatic high-risk individuals could potentially increase the proportion of patients with early-stage PDAC and thus improve overall survival. A well-established group of individuals at high risk are those with an inherited predisposition for the disease. About 5-10% of PDAC cases have either a positive family history for pancreatic cancer, a condition referred to as Familial Pancreatic Cancer (FPC), or an underlying germline mutation in specific genes associated with certain tumour syndromes that also predispose to PDAC.[2] Tumour syndromes that are relatively frequently associated with PDAC include Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome caused by a mutation in the *CDKN2A* gene and hereditary breast cancer caused by a mutation in the *BRCA2* gene in particular.[2]

A number of studies have described pancreatic surveillance in high-risk individuals, using screening tools such as endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP).[3] At an international multidisciplinary consensus meeting in 2011 on the surveillance and management of individuals at high risk for PDAC, indications for surgery of these individuals were addressed, but no recommendations were given regarding the extent of surgery, that is, partial or total pancreatectomy, in patients with a screen-detected PDAC.[3] This is an important issue because it seems very likely that a hereditary background increases the risk for a second primary cancer of the pancreas.

Here we describe two high-risk individuals who developed a second primary cancer after a partial pancreatectomy of an early-stage cancer. Based on these cases we discuss the pros and cons of a total pancreatectomy.

CASES

Patient 1 is a 62-year-old female with the Dutch '*p16-Leiden*' founder mutation in the *CDKN2A* gene (c.225_243del19; RefSeq NM_000077.4) and a medical history of melanoma at age 56. This patient was enrolled in the pancreatic surveillance program at Leiden University Medical Center in 2008. The first MRI showed a lesion in the head-corpus region of the pancreas, suspicious for an adenocarcinoma. The lesion was confirmed by CT scanning,

with no signs of distant metastases. A partial pancreaticoduodenectomy was performed. Histopathologic examination showed a well-differentiated (grade 1) adenocarcinoma of 5 mm, surrounded by PanIN1 lesions and an IPMN lesion. The resection margins were free of tumour and seven lymph nodes were unaffected (T1N0M0, UICC stage IA). A *KRAS* hotspot mutation in codon 12 was detected in the tumour (c.35G>T). This patient continued pancreatic surveillance. After 4 years and 6 months, a solitary lesion of 7 mm was found in the corpus-tail region with EUS. Cytological examination of an EUS-guided fine-needle aspirate showed atypical cells compatible with adenocarcinoma. Of note, no *KRAS* mutation was detected in these cells. CT scanning confirmed the presence of the lesion without evidence for distant metastases. A completion pancreatectomy with splenectomy was performed and histopathologic examination showed one small duct suspicious for adenocarcinoma surrounded by multifocal PanIN1-3 lesions. The resection margins of the specimen were free of tumour and 13 lymph nodes were unaffected (T1N0M0, stage IA). Fifteen months after completion pancreatectomy, the patient is alive with no evidence of disease.

Patient 2 is a 46-year-old female with a germline mutation in the *BRCA2* gene and three affected relatives with PDAC. In 1984, she developed a painless icterus; CT scanning and endoscopic retrograde cholangiopancreatography (ERCP) revealed a tumour in the pancreatic head. A partial pancreaticoduodenectomy was performed. Histopathologic examination showed a moderately differentiated (grade 2) adenocarcinoma of 22 mm. The resection margins were free of tumour and none of 14 lymph nodes were affected (T2N0M0, stage IB). In 1987, 2 years and 9 months later, the tumour marker CA 19.9 increased to 190 U/mL (normal <39 U/ml) and CT scanning revealed a tumour in the tail of the pancreas. A resection of the remnant pancreas was performed and histopathologic examination showed a poorly differentiated (grade 3) adenocarcinoma of 20 mm. The resection margins and eight lymph nodes were free of tumour (T2N0M0, stage IB). At the last follow-up, 28 years after completion pancreatectomy, the (currently 76-year-old) patient is alive with no evidence of PDAC.

DISCUSSION

This is the first report of the development of a second primary PDAC after partial resection of a first pancreatic tumour in patients with a genetically increased risk for the development of PDAC. The first patient carried a *CDKN2A* mutation and the second patient had a mutation in *BRCA2*; both gene defects are associated with the development of PDAC. Development of a metachronous second primary tumour in a remnant pancreas in

apparently *sporadic* PDAC cases has been previously described [4], but this is a very rare event, which is probably due to the poor survival of these patients.

The cases presented here raise a number of questions, the *first* of which is: did these patients actually develop a second primary or was the second tumour simply a local recurrence of the original tumour? Arguments that would support a second primary tumour rather than a local recurrence include: (1) a long interval between diagnoses of the tumours, (2) a location of the second tumour in another part of the pancreas (distant from resection lines), (3) differences in the pathology of the tumours, (4) different *KRAS* mutations in the tumours, and (5) both first and second tumours are early-stage without evidence for metastatic disease. The two cases comply with most of these criteria: (1) intervals between diagnoses were 4 years and 6 months in case 1 and 2 years and 9 months in case 2; (2) the location of the second tumour was distant from the resection lines in both cases; (3) in patient 2, the first tumour was a moderately differentiated (grade 2) adenocarcinoma, whereas the second tumour was a poorly differentiated (grade 3) adenocarcinoma; (4) in patient 1, the *KRAS* hotspot mutation detected in the first tumour was not detected in the cells obtained by cytology from the second tumour, suggesting a different aetiology; (5) in both cases, the first and second cancer were early-stage cancers (T1-2N0M0). Taken together, these findings suggest that these tumours are most likely second primary tumours.

A *second* important question is: what is the risk, in a patient with a genetic predisposition, of developing a second primary cancer after resection of a first PDAC? A previous study on surveillance outcomes for Dutch carriers of a *p16-Leiden* mutation reported that, while the program substantially increased the proportion of patients with resectable tumours, very few patients had a long survival.[5] This was echoed in the German surveillance program, where patients with a longer survival following resection of PDAC were also very rare.[6] The observation of a second tumour in these 'rare' (n=2) patients therefore suggests that a genetic predisposition contributes a substantial risk of developing a second primary tumour if the patient survives the first tumour. Moreover, the development of a second cancer within a relatively short follow-up time (2 to 4 years after the first tumour) also indicates substantial risk.

What are the implications of our findings for the surgical management of high-risk patients? Should we offer total pancreatectomy (TP) to all patients with a genetic predisposition and an early-stage cancer? A well-known disadvantage of TP is the development of 'brittle' diabetes which is associated with substantial morbidity. However, recent studies all concluded that TP is safe, with acceptable mortality and morbidity.[7,8] Studies that compared the perioperative mortality and morbidity of TP with partial pancreatectomy (PP, mostly

pancreaticoduodenectomy [PD]) produced more conflicting results (see *table*).[9-15] Some studies reported no significant difference in mortality and morbidity between TP and PD, whereas others reported a 1.5-3 fold increased risk of mortality and a (lesser) increased morbidity risk. Interestingly, two recent studies assessed quality of life (QoL) in TP cases compared with matched PD cases.[8,10] These studies demonstrated that QoL following TP is acceptable and similar to that reported for PD. Moreover, while brittle diabetes has a negative impact on QoL after TP, the level of impact is comparable to that of diabetes following PP or due to other causes. This conclusion was supported by another study that assessed QoL (without comparisons) in TP cases.[7] In light of these recent studies, the best approach may be to openly discuss the various advantages and disadvantages of TP with high-risk patients with early-stage PDAC and come to a decision together.

In conclusion, we describe two high-risk patients who developed a second primary PDAC two to four years after a partial pancreatic resection of an early-stage PDAC. In view of the acceptable perioperative mortality and morbidity risk of TP and an improvement of quality of life after TP in recent years, this type of surgery should be seriously considered in high-risk patients with an early-stage (screen-detected) tumour.

TABLE. Perioperative outcome of total pancreatectomy (TP) versus partial pancreatectomy (PP)

Reference	Cohort	Mortality (%)	Sign. (p-value)	Morbidity (%)	Sign. (p-value)
Schmidt *et al* [9]	TP n=33	6	n.s.	36	n.s.
	PD n=28	7		54	
Muller *et al* [10]	TP n=87	6	n.s.	31	n.s.
	PD n=87	3		23	
McPhee *et al* [11]	TP n=1,399	8.3	0.0002	n/a	n/a
	PD n=27,289	6.6		n/a	
Reddy *et al* [12]	*Period 1970-2007*				
	TP n=100	8	0.0007	69	<0.0001
	PD n=1,286	1.5		38.6	
	Subanalysis of period 2000-2007				
	TP n=53	*1.9*	*0.17*	*No significant change*	
	PD n=?	*1.2*			
Nathan *et al* [13]	TP n=376	8.6	0.09	n/a	n/a
	PP n=3,645	6.3		n/a	
Simons *et al* [14]	TP n=5,966	OR 2.90	<0.0001	OR 1.29	0.0025
	PD n=56,207	*Ref*		*Ref*	
Bhayani *et al* [15]	TP n=198	6.1	0.02	38	0.02
	PD n=6,314	3.1		30	

PD = Pancreaticoduodenectomy, OR = odds ratio, n.s. = not significant, n/a = not available

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