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### **Citation**

Onnekink, A. M., Michiels, N., Klatter, D. C. F., Oldenburg, L., Mieog, J. S. D., Vahrmeijer, A. L., ... Bonsing, B. A. (2023). Surgical outcomes after pancreatic surgery in patients with a germline CDKN2A/p16 pathogenic variant under surveillance. *British Journal Of Surgery*, 111(1). doi:10.1093/bjs/znad430

Version: Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).

# Surgical outcomes after pancreatic surgery in patients with a germline CDKN2A/p16 pathogenic variant under surveillance

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Pancreatic cancer surveillance programmes have shown encouraging results in detecting pancreatic cancer at an early stage, thereby enhancing the potential for curative treatment with surgical resection<sup>1</sup>. However, careful assessment of the need for early surgery and its associated risks is important, especially in the context of suspicious but indeterminate lesions. As there is a lack of data, the authors evaluated surgical outcomes in patients with suspected pancreatic cancer identified during surveillance.

Prospective data from patients participating in pancreatic surveillance with the germline Dutch founder CDKN2A/p16 pathogenic variant (PV), who have a 20% lifetime risk of pancreatic cancer, were analysed. Patients underwent surgery at the Leiden University Medical Centre, a high-volume centre for pancreatoduodenectomy (at least 70 procedures annually), between January 2000 and December 2022. The primary outcome was major complications within 30 days of surgery (Clavien–Dindo grade III or higher). Detailed methods are described in the [supplementary material](#).

A total of 32 CDKN2A PV carriers were included (13 men), with a mean(s.d.) age of 59(8) years and all with ASA grades of I or II ([Table S1](#)). Median tumour size was 15 (i.q.r. 6–30) mm and 15 of 32 tumours were located in the pancreatic head. Soft pancreatic texture was present in 21 of 32 tumours and median pancreatic duct diameter was 1 (i.q.r. 1–2) mm. Postoperative histopathology revealed malignancy in 24 of 32 patients ([Table S2](#)).

After pancreatoduodenectomy, 6 of 15 patients experienced major complications, all involving grade B/C postoperative pancreatic fistula (POPF) requiring hospital readmission and reintervention, including 2 reoperations ([Table 1](#)). Patients developing POPF all had a small pancreatic duct diameter (3 mm or less) and five of six patients had soft pancreatic tissue. Other procedure-related complications were postpancreatectomy haemorrhage (PPH,  $n = 4$ ), delayed gastric emptying (DGE,  $n = 3$ ), and bile leakage ( $n = 2$ ).

After distal pancreatectomy, major complications occurred in 2 of 16 patients (POPF,  $n = 1$ , PPH,  $n = 1$ ) ([Table 1](#)). Both patients required a reintervention (endoscopic/radiological) and one was

readmitted to hospital within 30 days. One patient underwent a requested total pancreatectomy for a tumour located in the pancreatic body without complications. None of the patients under surveillance died within 90 days of surgery. Surgical outcomes for malignant and non-malignant subgroups are described in [Table S3](#).

**Table 1 Short-term surgical outcomes for patients with a CDKN2A/p16 pathogenic variant under surveillance**

	Pancreatoduodenectomy ( $n = 15$ )	Distal pancreatectomy ( $n = 16$ )
Major complications*	6	2
90-day mortality	0	0
<b>Surgery-specific complications†</b>	7	2
POPF	6	1
DGE	3	0
PPH	4	1
Bile leakage	2	0
<b>Reinterventions needed</b>	6	2
Surgical	2	0
Radiological	6	2
Endoscopic	3	1
ICU admission	3	1
Hospital readmission‡	6	1
Textbook outcome	5	13
Duration of hospital stay (days), median (i.q.r.)	10 (8–30)	7 (5–11)
Adjuvant chemotherapy§	7 of 9	8 of 8

Age (years), median (i.q.r.) and Values are n (%) unless otherwise indicated. POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postoperative pancreatic haemorrhage. One patient who underwent total pancreatectomy was excluded from the stratified analyses of pancreatoduodenectomy and distal pancreatectomy. \*Complications of grade III or higher, according to the Clavien–Dindo classification, 30 days or less after surgery<sup>2</sup>. †All pancreatic surgery-specific complications were grade B/C according to International Study Group of Pancreatic Surgery and International Study Group of Liver Surgery criteria<sup>3–6</sup>. ‡Readmission 30 days or less after discharge. §Five patients who underwent pancreatic surgery before 2010 (2 pancreatoduodenectomy and 3 distal pancreatectomy) were excluded as adjuvant chemotherapy was not part of the standard of care.

Received: September 21, 2023. Revised: December 05, 2023. Accepted: December 07, 2023

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This study found a significantly higher incidence of POPF after pancreatoduodenectomy compared with recent benchmark data from the mandatory Dutch Pancreatic Cancer Audit (40 versus 19%)<sup>7</sup>. The observed discrepancy can be attributed to the pancreatic morphology of screen-detected lesions, as most tumours were small with soft pancreatic parenchyma and a small main duct (3 mm or less). Consequently, the majority of pancreatoduodenectomies in this study (13 of 15 procedures) were considered high-risk procedures with a calculated median risk of 44% of developing POPF, as determined by the alternative fistula risk score (median risk score 44, i.q.r. 25–60) (Table S4)<sup>8,9</sup>. This is in line with a previous cohort study<sup>10</sup>, which showed that 36% of patients undergoing pancreatoduodenectomy for intraductal papillary mucinous neoplasia (IPMN) developed POPF because of soft pancreatic tissue, and highlights the challenge in pancreatic surveillance of balancing the imperative of early surgical intervention for potentially malignant lesions against the increased risk of POPF.

## Funding

The authors have no funding to declare.

## Acknowledgements

M.E.v.L. and B.A.B. are joint last authors.

## Author contributions

Anke Onnekink (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft), Nynke Michiels (Conceptualization, Methodology, Validation, Visualization, Writing—review & editing), Derk C. F. Klatter (Conceptualization, Methodology, Validation, Visualization, Writing—review & editing), Lotte Oldenburg (Conceptualization, Project administration, Writing—review & editing), Sven Mieog (Writing—review & editing), Alexander Vahrmeijer (Writing—review & editing), Jeanin van Hooft (Project administration, Resources, Supervision, Writing—review & editing), Monique van Leerdam (Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing—review & editing), and Bert Bonsing (Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing—review & editing)

## Disclosure

The authors declare no conflict of interest.

## Supplementary material

Supplementary material is available at BJS online.

## Data availability

Requests for deidentified participant data can be made to the corresponding author and will be discussed by the study team.

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