

# STUDY PROPOSAL



## Detection, treatment and survival of pancreatic cancer recurrence in the Netherlands: a nationwide analysis

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### 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with a very poor prognosis, in part due to the development of disease recurrence in up to 80% of patients within two years after radical resection.<sup>1-4</sup> Despite the high incidence of recurrent pancreatic cancer, current national guidelines do not contain specific recommendations for surveillance after resection of pancreatic ductal adenocarcinoma.<sup>5,6</sup> The lack of Dutch or European guidelines regarding follow-up has led to different surveillance strategies among pancreatic surgeons in the Netherlands. A recent nationwide survey carried out under Dutch pancreatic surgeons showed that generally a symptomatic surveillance strategy is favored, consisting of regular outpatient visits without routine tumor marker testing or imaging.<sup>7</sup> The impact of this current practice on the detection and treatment of recurrent pancreatic cancer and overall survival has not been well established.

## 2. Aim

The aim of this study is to evaluate current surveillance strategies after primary resection of pancreatic cancer in the Netherlands, with regard to the detection and treatment of recurrent disease.

## 3. Intervention

Not applicable.

## 4. Sample size

All patients undergoing resection for primary pancreatic ductal adenocarcinoma between 2011 and 2016.

## 5. Study design

A retrospective observational cohort study in all DPCG-affiliated centers.

## 6. Primary outcome measures

- Incidence of PDAC recurrence
- Patterns of PDAC recurrence (asymptomatic vs. symptomatic; first site of recurrence; early vs. late recurrence)
- Treatment of PDAC recurrence

## 7. Secondary outcome measures

- Symptoms at time of (suspected) recurrence
- Performance score at time of recurrence detection
- Use of imaging procedures during follow-up
- Number of histologically confirmed recurrences
- Recurrence-free survival
- Post-recurrence survival
- Overall survival

## 8. Inclusion criteria

- Patients with PDAC confirmed by pathological examination
- Patients undergoing a pancreatic resection (PPPD, Whipple, distal pancreatectomy or total pancreatectomy)

## 9. Exclusion criteria

- Patients with 30-day postoperative mortality

## 10. Participating centers

All DPCG-affiliated hospitals.

## 11. Data collection

The following data will be collected: age, sex, BMI, ASA score, preoperative CA 19-9 level, operation procedure, resection margin status (R0/R1/R2), tumor differentiation, tumor size, TNM stage, total lymph nodes, positive lymph nodes, microscopic perineural invasion, microscopic perilymphatic invasion, adjuvant therapy, date start adjuvant treatment, time between surgery and start date adjuvant treatment, number of cycles adjuvant treatment received, use and type of imaging procedures, presence of recurrence, presence of histological evidence for recurrence and pathologic results, recurrence site, date of recurrence, symptomatic recurrence, asymptomatic recurrence, type of treatment after recurrence, date of operation, date of death, date of last follow-up.

Asymptomatic recurrence is defined as recurrent pancreatic cancer detected as an incidental finding following additional examination for other reasons or by imaging requested by the patient. If recurrent pancreatic cancer is discovered due to a significant patient-initiated complaint that is new or has been increased in severity or frequency, disease recurrence will be defined as symptomatic.

Patterns of recurrence are furthermore categorized using four categories: 1) isolated local recurrence: recurrence in the pancreatic remnant or in the surgical bed, such as soft tissue along the celiac or superior mesenteric artery, aorta or around the pancreatojejunostomy site; 2) isolated distant recurrence: recurrence restricted to a single organ or site; 3) local + distant recurrence: simultaneous occurrence of both isolated local recurrence and isolated distant recurrence; 4) multiple recurrence: recurrence at multiple distant sites and/or carcinomatosis.

Early disease recurrence is defined as recurrence < 10 months after surgery, late disease recurrence is defined as recurrence ≥ 10 months after surgery. This cutoff point was found to be the most significant value for showing differences in post-recurrence survival.

Overall survival (OS) and post-recurrence survival are defined as the time from the date of operation (OS) or the date of recurrence (post-recurrence survival) to either death from any cause or last follow-up. Recurrence-free survival (RFS) is defined as the time interval between the date of the operation and either date of recurrence or last follow-up if recurrence is not observed.

## 12. Statistical analyses

Descriptive statistics will be obtained. Continuous variables are expressed as median and range, unless specified otherwise, and categorical values as number (percentage). The proportion of patients receiving imaging procedures for each month of follow-up will be calculated by dividing the amount of patients receiving one or more imaging procedure(s) for the detection of recurrence by the amount of uncensored patients. Censoring occurs at date of recurrence, death, or last follow-up if recurrence does not occur. Kaplan-Meier curves are used to

estimate median OS, RFS and post-recurrence survival with corresponding 95% confidence intervals. Univariable and multivariable analyses will be performed using Cox proportional hazard models to identify potential predictive factors for post-recurrence survival. A two-tailed P value of <0.05 is considered to indicate statistical significance. Statistical analysis will be performed with SPSS statistical software, version 23.0 (SPSS Inc., Chicago, IL).

### 13. Co-authorships

Authorship will be based on international ICMJE guidelines. Next to the study team (L.A. Daamen, I.W.J.M. van Goor, V.P. Groot, M. Intven, N. Haj Mohammad, L.A.A. Brosens, H.C. van Santvoort and I.Q. Molenaar), the number of authors per centre will be based on number of pancreatic resections in the study period (2011-2016): 1 author per centre performing up to 100 pancreatectomies; 2 authorships per centre performing >100 pancreatic resections. The study coordinators will be first and second authors (Daamen and Groot) where project leaders will be shared senior authors (Molenaar and van Santvoort). Other co-authorship places will be awarded in accordance to international guidelines.

### 14. Quality control

Not applicable.

### 15. Study duration

Not applicable since it is a retrospective study.

### 16. Ethical approval

It is confirmed by the MREC UMC Utrecht that an official approval of this study is not required under the Medical Research Involving Human Subject Act (WMO). The data will be handled confidentially and anonymously. The handling of personal data will comply with the Dutch Personal Data Protection Act (De Wet Bescherming Persoonsgegevens). A subject identification code list will be used to link the data to the subject. These codes will not be based on the patient initials and birth date. The coordinating investigator will safeguard the key to this code. The data will be kept for a minimum of 15 years.

### 17. References

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