



**Karolinska
Institutet**

**Institutionen för klinisk vetenskap, intervention och teknik
(CLINTEC), Enheten för kirurgi**

Pancreatic fistula following pancreaticoduodenectomy

Risk assessment and early diagnosis

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras på engelska i föreläsningssal R 64,
Karolinska Universitetssjukhuset Huddinge

Onsdagen den 5 juni 2013, kl 13.00

av

Christoph Ansorge

Leg. läkare

Huvudhandledare:

Med. Dr. Ralf Segersvärd
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention
och teknik (CLINTEC), Enheten för kirurgi

Bihandledare:

Docent Lovisa Strömmer
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention
och teknik (CLINTEC), Enheten för kirurgi

Professor Jörgen Larsson
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention
och teknik (CLINTEC), Enheten för kirurgi

Fakultetsopponent:

Professor Jens Werner
University of Heidelberg, Germany
Department of General, Visceral and
Transplantation Surgery

Betygsnämnd:

Docent Malin Sund
Umeå Universitet
Institutionen för kirurgisk och perioperativ
vetenskap

Professor Anders Thorell
Karolinska Institutet
Institutionen för kliniska vetenskaper,
Danderyds sjukhus

Professor Per-Olof Nyström
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik (CLINTEC)

Stockholm 2013

Summary of the thesis

Pancreaticoduodenectomy (PD), a complex surgical procedure for resecting tumors of the pancreatic head, distal bile duct or periampullary region, is associated with a considerable morbidity. Postoperative pancreatic fistula (POPF), the main contributor, is caused by leakage from the pancreatico-enteric anastomosis and ranges from 15 to 26%. If not controlled promptly, POPF may lead to a complex postoperative course with septic or hemorrhagic complications, organ failure and increased mortality. Although multiple approaches to decrease POPF rates have been reported, an effective preventive strategy has not been found. The aims of this thesis were to study the contributing factors and early diagnostic markers of clinically relevant POPF, and to formulate predictive models that may facilitate clinical management of patients undergoing PD.

In **study I**, a prospective observational cohort study on 48 non-consecutive PD patients 2007-10, local metabolite changes and protease activation in the proximity of the pancreaticojejunostomy (PJ) were measured by microdialysis to investigate the pathophysiology of POPF. In patients subsequently developing POPF, high glycerol and lactate/pyruvate (LP) ratio levels, low glucose concentrations and presence of trypsinogen activation peptides were observed before any POPF symptoms appeared. The fact that glycerol level peaks preceded the elevations in LP ratios suggested that the early glycerol release in POPF patients was not initiated by local ischemia.

In **study II**, a prospective observational cohort study on 110 non-consecutive PD patients 2008-10, the predictive impact of a standardized intraoperative assessment of pancreatic consistency (PC) and pancreatic duct diameter (PDD) on the development of POPF was investigated. Combining both characteristics in a composite classification, the risk for POPF or fluid collections could be stratified as ‘high’ (softer PC and smaller PDD, incidence of associated morbidity 51%), ‘intermediate’ (softer PC or smaller PDD, 26%) or ‘low’ (no risk factors, 2%). Only patients with smaller PDD developed severe POPF.

In **study III**, a prospective observational cohort study on 195 consecutive PD patients 2008-10, the importance of POPF for PD-associated morbidity was evaluated by comparing the predictive impact of an intraoperative pancreatic risk assessment (IPRA) with the generally applicable “Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity” (POSSUM). Although the POSSUM-estimated risk corresponded with observed morbidity for the entire cohort, individual and grouped POSSUM risk estimates did not reveal any association with the incidence or severity of overall morbidity. However, the IPRA model identified patients with high POPF-risk and was even significantly associated with the incidence and severity of overall morbidity.

In **study IV**, a prospective observational cohort study on 315 consecutive PD patients 2008-12, the analysis of pancreatic amylase from intraabdominal drainage (DPA) as an early diagnostic marker of POPF following PD was evaluated. DPA at selected cut-off levels was proven to be superior to that of plasma pancreatic amylase in predicting clinically relevant POPF. A model combining DPA and C-reactive protein (CRP) had the highest POPF-predictive impact. Persistently raised CRP levels on POD 3 proved to be an independent indicator for subsequent POPF development.

In summary, standardized intraoperative pancreatic risk assessment (IPRA) constitutes a central tool for surgical decision making in the risk management of patients undergoing PD. It had a stronger predictive impact on the incidence and severity of overall postoperative morbidity than an established generally applicable risk adjustment model (POSSUM). Analyses of local metabolite concentrations or pancreatic amylase levels from intraabdominal fluids in the proximity of the PJ could serve as diagnostic markers for subsequent POPF development at an early subclinical stage.