Brief Clinical Report

ANNALS OF SURGERY OPEN

OPEN

Intraoperative Fluorescence Imaging During Robotic Pancreatoduodenectomy to Detect Suture-Induced Hypoperfusion of the Pancreatic Stump as a Predictor of Postoperative Pancreatic Fistula (FLUOPAN)

Prospective Proof-of-concept Study

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Background: A potential downside of robotic pancreatoduodenectomy (RPD) is the lack of tactile feedback when tying sutures, which could be especially perilous during pancreatic anastomosis. Near-infrared fluorescence imaging with indocyanine green (NIRF-ICG) could detect transpancreatic-suture-induced hypoperfusion of the pancreatic stump during RPD, which may be related to postoperative pancreatic fistula (POPF) grade B/C, but studies are lacking.

Methods: This prospective study included 37 patients undergoing RPD to assess the relation between pancreatic stump hypoperfusion as objectified with NIRF-ICG using Firefly and the rate of POPF grade B/C. In 27 patients, NIRF-ICG was performed after tying down the transpancreatic U-sutures. In 10 'negative control' patients, NIRF-ICG was performed before tying these sutures.

Results: Pancreatic stump hypoperfusion was detected using NIRF-ICG in 9/27 patients (33%) during RPD. Hypoperfusion was associated with POPF grade B/C (67% [6/9 patients] versus 17% [3/18 patients], $P = 0.026$). No hypoperfusion was objectified in 10 'negative controls'.

Conclusions: Transpancreatic-suture-induced pancreatic stump hypoperfusion can be detected using NIRF-ICG during RPD and was associated with POPF grade B/C. Surgeons could use NIRF-ICG to adapt their suturing approach during robotic pancreatico-jejunostomy. Further larger prospective studies are needed to validate the association between transpancreatic-suture-induced hypoperfusion and POPF.

Keywords: pancreatoduodenectomy, whipple, robotic surgery, fluorescence, indocyanine green, perfusion assessment, pancreatic fistula

INTRODUCTION

Postoperative pancreatic fistula (POPF) after robotic pancreatoduodenectomy (RPD) could be related to ischemia of the pancreatic stump due to excessive tension on surgical sutures.[1–3] Sutures can cause compression ischemia, leading to reperfusion injury, inflammation, and necrosis.[2–4] This is particularly important in robotic surgery, as haptic feedback is absent in the current systems and intraoperative force measurement tools are lacking.[5] Near-infrared fluorescence-based imaging with indocyanine green (NIRF-ICG) could be used to assess pancreatic stump perfusion, exerted by the transpancreatic U-sutures used during the pancreatico-jejunostomy. Studies assessing pancreatic stump hypoperfusion during pancreatoduodenectomy are currently lacking.

This prospective proof-of-concept study aimed to determine whether transpancreatic-suture-induced pancreatic stump hypoperfusion could be detected with NIRF-ICG and to assess whether this was related to POPF grade B/C.

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Disclosure: The authors state that they have no proprietary interest in the products named in this article.

This study was not preregistered in an institutional registry.

J.W.C.: Participated in research design, performance of research, data curation, data analysis, and writing of the article. S.L. and M.J.W.Z.: Participated in research design, data analysis, and writing of the article. O.R.B., F.D., S.F., and Z.V.F.: Participated in the performance of research, review and editing. M.H. and M.D.S.: Participated in research design, performance of research, review, and editing. M.D.S.: Participated in research design and performance of research. E.J.M.N.v.D.: Participated in review and editing and supervision. M.G.B.: Participated in research design, the performance of research, review and editing, and supervision.

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Annals of Surgery Open (2023) 4:e354

Received: 7 August 2023; Accepted 28 September 2023

Published online 29 November 2023

DOI: 10.1097/AS9.0000000000000354

MATERIALS AND METHODS

This study was approved by the Amsterdam UMC ethics committee (W20_042#20.151). Written informed consent was obtained from all participants.

Eligibility

Included were patients aged 18 years or older undergoing RPD at Amsterdam UMC between May 1, 2020, and September 31, 2022. Excluded were patients with allergies to ICG, iodide, or shellfish, pregnancy, lactation, hyperthyroidism, thyroid tumor, and severe renal failure (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2).

Anastomosis Technique

Two out of four senior pancreatic surgeons (O.B., F.D., S.F., and M.B.) performed all RPD procedures. One surgeon (M.B.) conducted a modified Blumgart end-to-side pancreatico-jejunostomy in every procedure.[6]

Fluorescence Technique

Perfusion assessment utilized the built-in Firefly fluorescence-imaging camera of the Da Vinci XI surgical system (Intuitive Inc., Sunnyvale, CA, USA). The ICG used was Verdye (Diagnostic Green GmbH, Aschheim-Dornach, Germany). ICG was administered according to the institutional protocol with a bolus dose of 0.1 mg/kg. Surgical videos in high-definition quality were stored in RVC Clinical Assistant (RVC Medical IT V.B., Amersfoort, The Netherlands).

Perfusion Assessment

First, a surgical gauze was placed in front of the liver to minimize fluorescence scattering from the liver. Next, ICG was administered, and the moment of the first arterial fluorescence in the common hepatic artery was noted. Hereafter, the fluorescence perfusion pattern of the pancreatic stump was assessed every 30 seconds up to 120 seconds after the first appearance of fluorescence. The perfusion of the pancreatic stump was scored intraoperatively by the surgical team as either 'normal perfusion' or 'hypoperfusion'. Six months after the inclusion of the last patient, the intraoperative images were reviewed independently by 2 pancreatic surgeons (O.B. and F.D.) to assess interrater reliability. Both reviewers were blinded for the initial intraoperative assessment and the presence of POPF grade B/C.

Suture Technique

The first 10 patients received transpancreatic U-sutures using Silk 2/0 as standard practice, thereby applying 'maximal' tension through the robotic system.[7] Hereafter, after observing several patients with pancreatic stump hypoperfusion, out of safety concerns, we discussed these findings and details of our suturing technique with the original proctors of the LAELAPS-3 program (M.E.H.). Based on their advice, our technique was altered to using a 'measured' tension approach when tying down the transpancreatic U-sutures in 17 patients, using less tension, with the aim to reduce the rate of hypoperfusion.

Negative Controls

In 10 patients the pancreatic stump was assessed before tying down the transpancreatic U-sutures to confirm that hypoperfusion was not induced by other factors, such as the pancreatic transection itself or the pancreatic stump mobilization.

Definitions and Terminology

The pancreatic stump was defined as the area between the pancreatic transection plane and the transpancreatic sutures. Normal perfusion was defined as similar fluorescence in the pancreatic stump and the rest (left side) of the pancreas after tying down the transpancreatic sutures. Pancreatic stump hypoperfusion was defined as a partially (patchy) or completely absent fluorescence signal in the pancreatic stump as compared with the rest of the pancreas. Major complication was defined as Clavien-Dindo grade ≥3.[8] POPF was graded according to the 2016 definition of the International Study Group for Pancreatic Surgery (ISGPS), including only clinically relevant POPF, ie, grade B/C.[9]

Statistical Analysis

IBM SPSS Statistics for Windows version 28.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Normally distributed continuous data were presented as mean with standard deviations (SD) and compared using the two-tailed Student *t* test. Non-normally distributed continuous data were presented as median with interquartile ranges (IQR) and were compared using the Mann-Whitney U test. Categorical data were presented as frequencies with percentages and were compared using the χ^2 test or Fisher exact test, as appropriate. A two-tailed *P* value <0.05 was considered statistically significant. Cohen's *k* statistic was used to determine interrater reliability. No sample size calculation was performed since this was an exploratory proof-of-concept study.

RESULTS

Overall, 37 patients undergoing RPD were included. The median ICG dose in all 37 patients was 8.0 mg (IQR 7.5–9.0), and the first arterial fluorescence appeared at 21.5 seconds (16.3–33.8) (Table 1). Pancreatic stump perfusion became stable in all patients before 90 seconds (ie, no differences were seen between 90 and 120 seconds). No adverse events occurred due to ICG administration.

Assessment Cohort

In the 27 patients undergoing RPD, suture-induced hypoperfusion of the pancreatic stump was observed in 33% (9/27 patients) (see Fig. 1 and supplemental video). Among these 9 patients with hypoperfusion, 6/9 (67%) developed grade B/C POPF, compared with 3/18 (17%; *P* = 0.026) in those without hypoperfusion (odds ratio 10.0). The likelihood ratio for POPF was 6.694; *P* = 0.010, which remained consistent when taking either grade B or C severity of POPF into account: 7.567; *P* = 0.023 (No-POPF/grade B/grade C: 3/5/1 *vs* 15/3/0).

During the course of the study, in 5 of the first 10 patients (50%), pancreatic stump hypoperfusion was observed. Of these 5 patients with hypoperfusion, 80% (4/5 patients) developed grade B/C POPF. Conversely, none (0/5) of the patients without hypoperfusion developed POPF. After which, we discussed this worrying finding with our original proctors (M.E.H.) and changed to a 'measured tension' approach in the next 17 patients. In these 17 patients, we observed hypoperfusion in 4 patients (24%). In this small sample size, this difference did not reach statistical significance (5/10, 50% *vs* 4/17, 24%; *P* = 0.219).

Negative Controls

In 10 patients, to confirm that the observed pancreatic stump hypoperfusion was attributable to the transpancreatic U-sutures

TABLE 1.

Baseline Characteristics of 37 Patients Undergoing Robotic Pancreatoduodenectomy, With and Without Pancreatic Stump Hypoperfusion

Baseline Characteristics	Total Cohort (n = 37)	Assessment Cohort (n = 27)	Hypoperfusion (n = 9)	No hypoperfusion (n = 18)	P value
Age (years), median [IQR]	71 (60–77)	71 (59–77)	70 (65–75)	73 (58–77)	0.718
Male sex, n (%)	26 (70)	18 (67)	5 (56)	13 (72)	0.423
Body mass index >25 kg/m^2, n (%)	22 (59)	18 (67)	5 (56)	13 (72)	0.423
ASA ≥III, n (%)	11 (30)	6 (22)	4 (44)	2 (11)	0.136
Tumor types, n (%)					0.809
IPMN	10 (27)	8 (30)	3 (33)	5 (28)	
Distal cholangiocarcinoma	8 (22)	4 (15)	1 (11)	3 (17)	
Vater's ampulla carcinoma	6 (16)	6 (22)	2 (22)	4 (22)	
Ductal adenocarcinoma	5 (14)	3 (11)	2 (22)	1 (6)	
Neuroendocrine	4 (11)	2 (15)	0 (0)	2 (11)	
Duodenal adenocarcinoma	2 (5)	2 (7)	1 (11)	1 (6)	
No tumor/chronic pancreatitis	2 (5)	2 (7)	0 (0)	2 (11)	
Tumor size (mm), median [IQR]	26 (16–39)	21 (15–39)	25 (18–41)	27 (14–39)	0.943
Previous abdominal surgery, n (%)	9 (24)	5 (19)	2 (22)	3 (17)	1.000
Updated FRS (%), median [IQR]	27 (20–41)	27 (20–47)	27 (22–47)	26 (18–52)	0.879
Intraoperative variables					
Pancreatic duct* (mm), median [IQR]	3 (2.5–4.5)	3 (2–4)	3 (2.5–4)	3 (2–4.3)	0.853
Hard texture, n (%)	16 (44)	13 (50)	4 (50)	9 (50)	1.000
Missing, n	1	1	1		
Fluorescence (sec), median [IQR]†	22 (16–34)	20 (14–28)	27 (12–33)	20 (15–25)	0.305
Blood loss (mL), median [IQR]	200 (100–350)	200 (100–350)	200 (50–250)	200 (100–425)	0.178
Postoperative variables					
Clavien-Dindo grade ≥3, n (%)	19 (51)	15 (56)	5 (56)	10 (56)	1.000
POPF grade B/C	12 (32)	9 (33)	6 (67)	3 (17)	0.026
PPH grade B/C	5 (14)	5 (19)	3 (33)	2 (11)	0.295
Delayed gastric emptying grade B/C	4 (11)	4 (15)	1 (11)	3 (17)	1.000
Surgical site infection grade B/C†	17 (46)	12 (44)	4 (44)	8 (44)	1.000
Biliary leakage grade B/C	4 (11)	4 (15)	1 (11)	3 (17)	1.000
Reintervention, n (%)					0.866
Radiological	17 (46)	13 (48)	4 (44)	9 (50)	
Surgical	2 (5)	2 (7)	1 (11)	1 (6)	
Readmission 30-days, n (%)	11 (30)	9 (33)	1 (11)	8 (44)	0.193
Mortality, n (%)	1 (3)	1 (4)	1 (11)	0 (0)	0.333

*Diameter.

†Time from intravenous administration to first arterial fluorescence.

ASA indicates American Society of Anesthesiologists criteria; FRS, Fistula Risk Score; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; mm, millimeter; n, number; sec, seconds; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrhage.

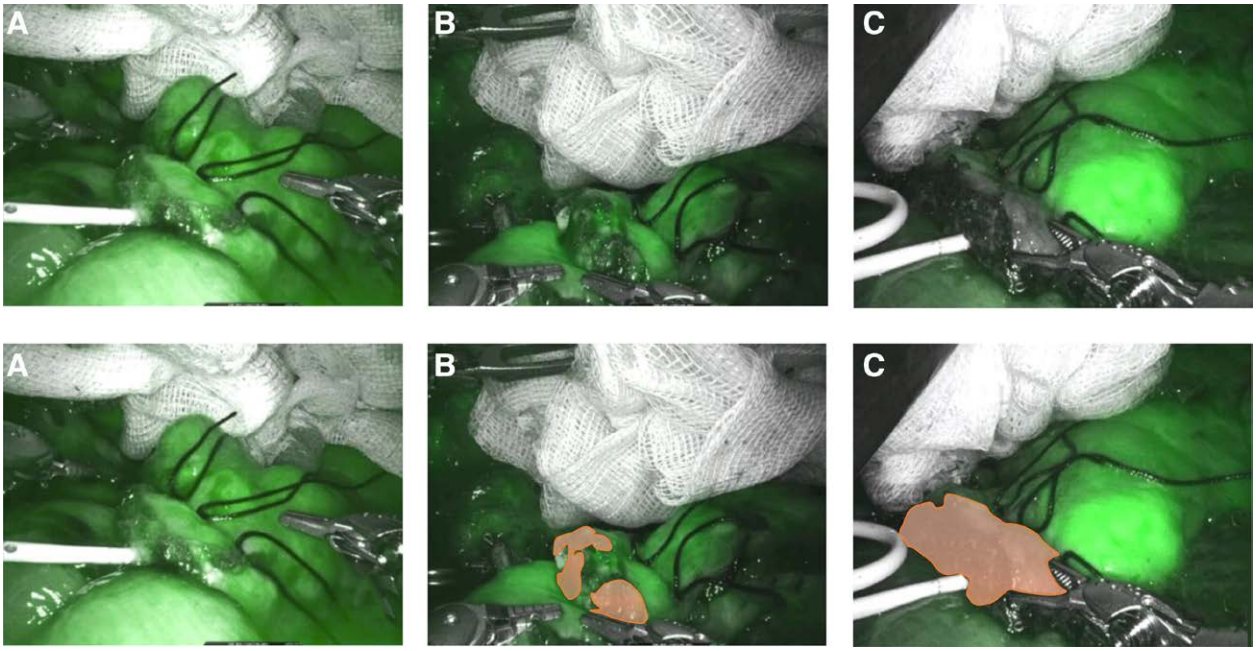

FIGURE 1. Examples of fluorescence in the pancreatic stump in 3 different patients (top) and annotations depicting hypoperfusion (bottom). A, Patient without pancreatic stump hypoperfusion. B, Patient with patchy-appearance pancreatic stump hypoperfusion. This patient developed a POPF grade B requiring radiological drainage. C, Patient with uniform-appearance pancreatic stump hypoperfusion. This patient developed POPF grade B, postpancreatectomy hemorrhage, and delayed gastric emptying.

and not to other factors, a perfusion assessment was performed before tying the sutures. In none of these 10 'negative control' patients, hypoperfusion was observed. The rate of POPF grade B/C in this group was 30% (Grade B POPF 3/10 patients).

Review Images

There was moderate interrater reliability between the initial intraoperative assessment and the 2 blinded assessors (k_1 = 0.41; P = 0.012 and k_2 = 0.51; P = 0.002). There were high levels of agreement in determining the absence of hypoperfusion (k_1 = 85.7% and k_2 = 88.9%) and moderate levels for determining hypoperfusion (k_1 = 55.6% and k_2 = 60.0%). Interrater reliability between the 2 blinded assessors was high (k = 0.79; P < 0.001).

DISCUSSION

This proof-of-concept study demonstrated that NIRF-ICG can be used to detect transpancreatic-suture-induced pancreatic stump hypoperfusion during RPD. Hypoperfusion was associated with an increased rate of POPF grade B/C (67% *vs* 17%; P = 0.026), as compared with patients without hypoperfusion. Interestingly, when the pancreatico-jejunostomy suturing technique was adapted during the study from 'maximal' to 'measured' tension on the transpancreatic sutures, a nonsignificant reduction in the rate of pancreatic stump hypoperfusion was observed (50%–24%).

Previous prospective studies investigating nonsuture-related perfusion of the pancreatic stump during open pancreatoduodenectomy also reported that blood supply to the pancreatic stump was associated with the rate of POPF.[10,11] Unfortunately, multivariable logistic regression analysis to assess the value of hypoperfusion in relation to other known risk factors for POPF was not possible due to the low number of events.

Surgeons should exercise caution when tying the transpancreatic U-sutures during the modified Blumgart approach in RPD due to the potential risk of pancreatic stump hypoperfusion. This is clearly not different from traditional open surgery, but can be especially perilous in robotic surgery where haptic feedback is lacking. Further larger prospective studies in patients undergoing RPD are required to confirm these findings. In conclusion, NIRF-ICG is a fast, safe, and easy-to-use tool to visualize hypoperfusion of the pancreatic stump during RPD, especially given the built-in Firefly fluorescence-imaging camera of the Da Vinci XI surgical system. Future studies should quantitatively analyze the NIRF-ICG patterns (ie, multiple grades of hypoperfusion) and validate its use during RPD to confirm the relation with POPF grade B/C.

ACKNOWLEDGMENTS

We thank the operating theater staff in both hospital locations of Amsterdam UMC, especially S.I. Sussenbach and F. de Graaf.

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