Pancreatoduodenectomy with colon resection for cancer: A nationwide retrospective analysis

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Background. *Microscopically radical (R0) resection of pancreatic, periampullary, or colon cancer may occasionally require a pancreatoduodenectomy with colon resection (PD-colon), but the benefits of this procedure have been disputed, and multicenter studies on morbidity and oncologic outcomes after PD-colon are lacking. This study aimed to assess complications and survival after PD-colon.*
Methods. *Patients who had undergone PD-colon from 2004–2014 in 1 of 13 centers were analyzed retrospectively. Ninety-day morbidity was scored using the Clavien-Dindo score and the Comprehensive Complication Index (CCI, 0 = no complications, 100 = death). Survival was analyzed per histopathologic diagnosis.*
Results. *After screening 3,218 consecutive PDs, 50 (1.6%) PD-colon patients (median age 66 years [interquartile range 55–72], 33 [66%] men) were included. Twenty-three (46%) patients had pancreatic ductal adenocarcinoma (PDAC), 19 (38%) other pathology, and 8 (16%) colon cancer. Ninety-day Clavien-Dindo ≥3 complications occurred in 30 (60%) patients without differences per diagnosis (P > .99); mean CCI was 39 (standard deviation 27). Colonic anastomosis leak, pancreatic fistula, and 90-day mortality occurred in 3 (6%), 2 (4%), and 4 (8%) patients, respectively. A total of 11/23 (48%) patients with PDAC and 8/8 (100%) patients with colon cancer underwent an R0 resection. Patients with PDAC had a median postoperative survival of 13 months (95% confidence interval = 5–21). One-, 3-, and 5-year cumulative survival was 56%, 21%, and 14%, respectively. Median survival after R0 resection for PDAC was 21 months (95% confidence interval = 6–35). All patients with colon cancer were alive at end of follow-up (median 24 months [95% confidence interval = 9–110]).*
Conclusion. *In this retrospective, multicenter study, PD-colon was associated with considerable complications and acceptable survival rates when a tumor negative resection margin was achieved. (Surgery 2016;160:145-52.)*

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There are no conflicts of interest to disclose.

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Accepted for publication February 21, 2016.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2016.02.022

Microscopically radical (R0) tumor resection is the only chance for cure in patients with periampullary or colon cancer.[1-9] In patients with pancreatic cancer, the potential of an R0 resection is mainly determined by the extension of the tumor, which can be subdivided into localized and regional diseases. Localized pancreatic disease is defined as a tumor confined to the pancreas, which is usually technically

resectable.[10,11] Regional pancreatic disease is defined as a tumor invading structures adjacent to the pancreas. In recent years, the criteria for tumor resectability have shifted due to advances in operative techniques.[12-16] Consequently, operative resection and survival in patients with regional periampullary disease have improved significantly.[10] For colon cancer, the criteria have been extended as well, and postoperative outcomes are also improving due to developments in perioperative care.[17,18]

Several reports show an underutilization of operative resection for the treatment of pancreatic cancer.[10,19,20] While there is clearly room for improvement, there is no consensus on the extent of an operation in the case of ingrowth of pancreatic adenocarcinoma into the (meso)colon. In these patients, a pancreatoduodenectomy (PD) with colon resection (PD-colon) may be required to achieve R0 resection margins.[21,22] PD-colon may also be indicated for other malignant periampullary tumors growing into the (meso)colon such as for distal bile duct-, ampullary-, or duodenum carcinomas. Potentially, the same applies to colon cancer growing into the periampullary region, but the clinical benefits of PD-colon for these indications are unclear.[23-30]

The International Study Group on Pancreatic Surgery (ISGPS) has stated that specific conclusions on outcomes of extended multivisceral resections for pancreatic cancer are hampered by a lack of data.[15] Two registry studies found PD-colon to be an independent predictor of increased morbidity, as compared with PD alone, but morbidity after PD-colon was not specifically reported.[31,32] Survival after PD-colon (stratified by histopathologic diagnosis) has only been reported in 3 single-center studies on PDAC treatment[21,30,33] and in 2 single-center studies on colon cancer treatment,[27,28] including fewer than 14 patients per study.

Large multicenter series on complications and survival after PD-colon are lacking, but these data are needed to determine whether a PD-colon should be performed in patients with tumors involving both periampullary and colon structures. This study aimed to describe complications and survival after PD-colon for cancer on a nationwide level.

METHODS

Study design. A retrospective, multicenter cohort study was performed in patients who had undergone a PD-colon between January 1, 2004 and September 1, 2014 in 1 of 13 centers of the Dutch Pancreatic Cancer Group. Excluded were children (<18 years of age); patients in whom PD-colon was performed for a double tumor, metastasis, or secondary tumor; patients in whom the indication for colon resection was not related to PD (pancreatic cancer with a simultaneous solitary appendicitis); and patients with missing or incomplete operative records.

Children were excluded because they are not representative of the main population with pancreatic, periampullary, and colon tumors in regard to their comorbidities, life expectancy, and histopathology.[34,35] Patients with double tumors were excluded because their oncologic prognosis differs from single tumors and because they all were preoperatively planned as multivisceral resection. The medical ethics review committee of the Academic Medical Center (Amsterdam, The Netherlands) waived the need for informed consent due to the retrospective and anonymous nature of this study.

Definitions. PD-colon was defined as a PD with colon resection. For PD, the definition of the ISGPS was used.[15] Resection margins, including transection and all circumferential margins, were defined according to the recommended method developed by the Royal College of Pathologists[36] and classified into R0 (microscopically radical; distance margin to tumor ≥1 mm), R1 (macroscopically radical; distance margin to tumor <1 mm), and R2 (macroscopically positive margin). The TNM classification of the American Joint Committee on Cancer (AJCC, 7th edition) was used for tumor grading.[37]

Complications were scored according to the Clavien-Dindo grading system for operative complications.[38] The Comprehensive Complication Index (CCI, 0 = no complication, 100 = death) was calculated for each patient using Clavien-Dindo scores of every single complication. For this calculation, the formula $CCI = \sqrt{(\sum MRV_{physician} \times MRV_{patient})}/2$ was used, where $MRV_{physician}$ was the median reference value of physicians and $MRV_{patient}$ was the median reference value of patients.[39]

For CCI calculations, different complications leading to a simultaneous equal treatment were recorded as separate cumulative complications. Postoperative pancreatic fistulas (POPF) were scored using the International Study Group on Pancreatic Fistula (ISGPF) definition.[40] Postpancreatectomy hemorrhage and delayed gastric emptying were scored using the ISGPS definitions.[41,42] Bile leak was scored using the International Study Group on Liver Surgery (ISGLS) definition.[43] Gastrojejunostomy (or duodenojejunostomy) leak and colon anastomotic leak were recorded if a defect was seen on

imaging, during reoperation, or during autopsy.[44] Operative site infections were scored using the Centers for Disease Control and Prevention definition.[45]

Data collection. Eligible patients were selected by screening all operative reports of PDs for additional colon resections. Data of these patients were collected from records and patient charts with daily notes. Collected data included baseline characteristics, intraoperative outcomes, pathology outcomes, and postoperative outcomes (including complications, hospitalization parameters, and survival). Only ISGPS/ISGPF/ISGLS grade B/C complications were considered relevant. Survival status of all patients was assessed on June 10, 2015, using the Dutch municipal personal records database. All data were stored and processed anonymously.

Statistical analysis. Statistical analysis was performed using SPSS Statistics for Windows (Version 20.0; IBM, Armonk, NY). Dichotomous data were presented as proportions. Continuous data were presented as means with standard deviations (SDs) for normally distributed data or as medians with interquartile ranges (IQRs) for non-normally distributed data. The null hypothesis of normality was rejected when plotted histograms suggested a non-normal distribution. The χ^2 test, Fisher exact test, Student *t* test, and Mann-Whitney *U* test were used as needed to find differences between groups. Kaplan-Meier survival analyses were used to extract postoperative median survival and 1-, 3-, and 5-year cumulative survival. Survival data were compared between groups using the log-rank test and were reported as medians with 95% confidence intervals (CIs).

RESULTS

Patient selection. A total of 3,275 PDs were performed in 13 centers. Operative records of 3,218 PDs were screened. PD-colon was performed in 71 (2%) patients. In total, 21 of these patients were excluded: 12 patients because of the presence of synchronous periampullary and colon tumors, 5 patients because the resected tumor was a metastasis, 2 patients because no tumor was suspected before the operation, 1 patient because of age (<18 years), and 1 patient because the indication for colon resection was not related to the indication for PD. Therefore, 50 (1.6%) patients were included in this study.

Baseline characteristics. Median age at operation was 66 years (55–72), and 33 patients were men (66%), see Table I. Histopathologic diagnosis was PDAC in 23 (46%) patients and colon cancer in 8 (16%) patients. In 2/40 (5%) patients with pancreatic or periampullary cancer, tumor involvement of the mesocolon (but not of the colon itself) was seen on preoperative imaging. In 7/9 (78%) patients with a tumor arising from the colon, involvement of periampullary structures was seen on preoperative imaging.

Table I. Baseline characteristics

	N = *50*	*Valid % or IQR*
Age (y), median	66	55–72
Male sex, *n* (%)	33	66
Histopathologic diagnosis		
Pancreatic ductal adenocarcinoma	23	46
Colon adenocarcinoma	8	16
Ampullary carcinoma	4	8
Duodenal adenocarcinoma	4	8
Gastroduodenal ulcer*	1	2
Other malignancy†	10	20
History of malignancy‡	9	18
History of an abdominal operation	25	50
Comorbidity	35	70
Cardiovascular	21	41
Pulmonary	4	8
Endocrine	13	26
Gastrointestinal	9	18
Other§	7	14
Body mass index (kg/m^2), median	23	21–25
ASA score		
1	4	9
2	30	65
3	11	24
4	1	2
Unknown ASA score	4	—
Neoadjuvant therapy	5	10

*In this patient, a PD-colon was performed because of suspected malignancy; however, the mass appeared to be an ulcer on pathologic examination.
†Including acinic cell carcinoma of the pancreas (1), solid pseudopapillary neoplasm of the pancreas (1), paraganglioma (1), medullary carcinoma (2), distal bile duct adenocarcinoma (1), gastrointestinal stromal tumor (2), pancreatic neuroendocrine tumor (1), and carcinoma of unknown origin (1).
‡Including renal cell carcinoma, nefroblastoma, colon carcinoma, pulmonary carcinoma, carcinoma of the prostate, seminoma, and a coexisting chronic lymphocytic leukemia.
§Including porphyria cutanea tarda, renal failure, hemochromatosis, chronic lymphocytic leukemia, thalassamia, and situs inversus.
ASA, American Society of Anesthesiologists; *IQR*, interquartile range.

Operative outcomes. Antibiotic prophylaxis consisted of a single intravenous shot of cefazolin (Kefzol) and metronidazole (Flagyl) in 96% of cases (*n* = 48); mechanic or antibiotic bowel preparation was not used routinely. In most cases (*n* = 40, 80%), PD-colon involved a right hemicolectomy (Table II). Colon resections were performed because of (expected or observed) colon ischemia after resection of the mesocolon (46%), tumor attachment to the colon (28%), primary

Table II. Operative outcomes

	N = *50*	*Valid % or IQR*
Vessel resection	16	32
PV/SMV	13	26
Inferior vena cava	3	6
Type of colectomy		
Right hemicolectomy*	40	80
Partial colectomy†	9	18
Total colectomy	1	2
Colon reconstruction		
Primary anastomosis or sutures‡	47	96
End ileostomy	2	4
Reasons for colectomy		
Mesocolon ingrowth	23	46
Tumor attachment or ingrowth	14	28
Colon tumor	8	16
Adhesiolysis	3	6
Other§	2	4
Additional organ resection		
Right kidney	3	6
Operative time (min), median	342	271–436
Intraoperative blood loss (mL), median	873	500–1625
Resection margins for PDAC patients		
R0	11	48
R1	10	43
R2	2	9
Resection margins for colon carcinoma patients		
R0	8	100

*Including one hemicolectomy of the ascending colon in a patient with situs inversus.
†Wedge resection, resection of transversum, flexura lienalis, or flexura hepatica.
‡One patient received a deviating stoma in combination with the primary anastomosis. The type of colon reconstruction was unknown for 1 patient.
§An accidental clamp injury of the colon in 1 patient and (meso)colon inflammation due to pancreatitis in 1 other patient with a distal bile duct tumor.
IQR, Interquartile range; *PV*, portal vein; *SMV*, superior mesenteric vein; *PDAC*, pancreatic ductal adenocarcinoma; *R0*, microscopically radical resection margins (distance margin to tumor ≥1 mm); *R1*, macroscopically radical resection margins (distance margin to tumor <1 mm); *R2*, macroscopically positive resection margin.

colon cancer (16%), or adhesiolysis, which went along with subsequent colon injury (6%).

PD-colon was performed en bloc in 23 (60%) patients. A separate PD and colectomy were performed in 19 (40%) patients, of which the majority (74%) was performed because of colon ischemia after mesocolon resection. Venous resection (portal vein, superior mesenteric vein, or inferior vena cava) was performed in 32% of cases. None of the patients underwent additional arterial resection. Median operative time was 342 minutes (IQR 271–436), and median operative blood loss was 873 mL (IQR 500–1624). At histopathologic examination, R0 resection was ascertained in 66% (n = 33), R1 resection in 26% (n = 13), and R2 resection in 8% (n = 4) of all patients. The R0 resection rates were significantly different for patients with PDAC and patients with colon cancer (11/23 [48%] and 8/8 [100%], respectively; P = .01).

Postoperative outcomes. During the 90-day postoperative period, 60% of patients experienced a Clavien-Dindo ≥3 complication (Table III), without a significant difference between patients with PDAC and colon cancer (13/23 [57%] vs 5/8 [63%]; P > .99). The median 90-day CCI was 35 (IQR 22–57). Furthermore, no significant difference was seen between these groups regarding the mean CCI (38 [SD 23] vs 30 [SD 19], respectively; P = .37).

Four patients (8%) died within 90 days after the operation; in 3 patients (6%), death was a result of postoperative complications. No difference between PDAC and colon cancer patients was found for 90-day mortality (1/23 [4%] vs 0/8 [0%], respectively; P > .99). One patient died due to PD-colon–related complications on postoperative day 331. The most frequent complications were delayed gastric emptying (n = 27, 54%), operative site infection (n = 17, 34%) and chyle leak (n = 10, 20%). POPF occurred in 2 patients (4%), and of the 47 patients who had a colon anastomosis, 3 patients (6%) had a colon anastomosis leak.

Survival. Specific survival analyses for other histopathology besides PDAC and colon cancer were considered inappropriate because of small patient groups. Survival curves for patients with PDAC and for patients with colon cancer are shown in the Figure. Patients with PDAC had a median postoperative survival of 13 months (95% CI 5–21) and a 1-, 3-, and 5-year postoperative cumulative survival of 56%, 21%, and 14%, respectively. Median survival after R0 resection was 21 months (95% CI 6–35) vs 12 months (95% CI 9–15) after R1/R2 resection (P = .88). Median survival of patients with PDAC who received adjuvant chemotherapy treatment (n = 10, gemcitabine [Gemzar]) was 37 months (95% CI 15–59) vs 11 months (95% CI 10–13) in patients not receiving chemotherapy (P = .005). In patients with colon cancer, 1-, 3-, and 5-year postoperative cumulative survival was 100%, with all patients alive at the end of follow-up (median 24 months [95% CI 9–111]).

DISCUSSION

In this retrospective, multicenter study, PD-colon for pancreatic, periampullary, or colon

Table III. Postoperative outcomes

	N = *50*	*Valid % or IQR or SD**
Clavien-Dindo score		
None	7	14
Mild (I-II)	13	26
Severe (III-IV)	27	54
Lethal (V)	3	6
Delayed gastric emptying	27	54
Grade B	11	—
Grade C	16	—
Operative site infection	17	34
Superficial or deep incisional	11	—
Organ/space	8	—
Chyle leak	10	20
Pneumonia	5	10
Sepsis	5	10
Diabetes mellitus	5	12
Bile leak	4	8
Grade B	2	—
Grade C	2	—
Colon anastomosis leak†	3	6
Gastrojejunostomy leak	2	4
Unknown gastro-/duodeno-jejunostomy/colon leak	1	—
Postoperative pancreatic fistula	2	4
Grade B	0	—
Grade C	2	—
Postoperative pancreatitis	2	4
Postpancreatectomy hemorrhage	1	2
Grade B	0	—
Grade C	1	—
90-day CCI, mean	39	±27
Complication-induced ICU stay‡	15	30
Postoperative hospital stay, median‡	21	11–42
Readmission <90 days after discharge	12	24
Adjuvant therapy	18	40

*Standard deviation for mean values; interquartile range for median values.
†Among the 47 patients with a primary colon anastomosis or sutures.
‡Excluding readmissions.
IQR, Interquartile range; *SD*, standard deviation; *CCI*, comprehensive complication index; *ICU*, intensive care unit.

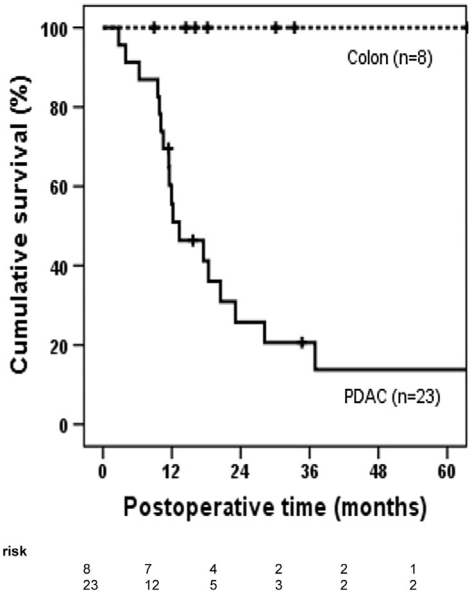

Fig. Kaplan-Meier curves of patients who underwent pancreatoduodenectomy with colon resection for pancreatic ductal adenocarcinoma (PDAC, *solid line*) or colon cancer (Colon, *dotted line*). Censored cases are indicated on the curves as *small horizontal tick marks*. Group comparison using a log-rank test gave $P = .003$.

cancer was a rare procedure, and it was associated with considerable complication rates but an acceptable postoperative survival when a tumor-negative resection margin was achieved. PD-colon for PDAC had a 48% R0 resection rate and a 5-year cumulative survival of 14%. PD-colon for colon cancer had a 100% R0 resection rate and a 100% cumulative survival after 24 months of follow-up. This is the largest series on PD-colon to date in which both operative complications and cancer-specific survival for PD-colon are reported.[21,27-30]

Two large retrospective studies found increased 30-day major morbidity and mortality rates in 159 PD-colon patients as compared with more than 9,900 PD patients from the ACS-NSQIP database,[31,32] but hepato-pancreato-biliary–specific complications, standardized severity scores, and long-term survival data were missing. Only Alvarado-Bachman et al[33] and Temple et al[29] have used the Clavien-Dindo score to define complication severity after PD-colon in 9 and 28 patients, respectively. Compared to the largest series by Temple et al,[29] the present series showed a higher major complication rate (60% vs 25%) but a similar 90-day mortality rate (8% vs 7%).

Temple et al[29] also compared these 28 PD-colon patients with 607 patients who had undergone PD alone and found neither differences for major complications nor for hepato-pancreato-biliary–specific complication rates between groups. When comparing complications from our series with other reports on PD, the 90-day mortality rate,[29] major complication rate,[29] ISGPS grade B/C delayed gastric emptying rate,[46] operative site infection rate,[31] and chyle leak rate[47] for PD-colon appeared relatively high, but the ISGPF grade B/C POPF[46] rate and ISGPS grade B/C postoperative hemorrhage rate[31,46] appeared at least comparable for PD-colon and PD.

A previous nationwide analysis in The Netherlands showed an in-hospital mortality of 6% in 2,155 PD patients, which seems similar to the 90-day mortality rate of 6% in the present PD-colon study.[48] Colon anastomotic leakage is a serious and potentially fatal complication after colon resection.[49-51] In this series, it occurred in 6% of patients after PD-colon, which is similar to the reported 7% from a previous nationwide study on patients after colon resection alone for colon cancer.[51-53] Although deviating stomas have been reported to reduce the risk of leak of the colon anastomosis[51] and end-colostomy avoids the risk of leak, the present study shows good results for patients with a primary anastomosis. This suggests that similar criteria for the type of colon reconstruction can be applied to PD-colon as well as to colon resection alone, such as a routine primary anastomosis and only end-colostomy in high-risk patients.[49,50,54,55]

Although survival for distal bile duct, duodenal, and colon cancer and PDAC differ significantly, operative outcomes for PD-colon would presumably account for similar short-term operative risks regardless of the preoperative indication.[56-58] The 14% 5-year cumulative survival after PD-colon for PDAC in the current study is worse than the reported 24% after PD alone for the same indication.[46]

Despite the operative procedure, PD-colon may be performed for more aggressive tumors, resulting in a somewhat lower survival.[20,59] Nevertheless, the difference between survival seems to correspond to the difference in R0 rates (48% PD-colon and 81% PD).[46] The present study shows a median survival after PD-colon for PDAC of 21 months in the case of R0 resection versus 12 months in the case of R1/R2 resection. PD-colon should only be performed for PDAC when an R0 resection can be obtained; this seems to be more challenging for PD-colon than PD alone.

A colon resection is a common procedure for the treatment of colon cancer and has a 74% 5-year cumulative survival.[8] The 100% survival in 8 patients with PD-colon for colon cancer seems comparable to a standard colon resection.

There are, however, some limitations that have to be considered when interpreting the results of this study. First of all, because of its observational design, which is inherent to the low incidence of PD-colon, outcomes are likely to be influenced by selection and information bias. Subgroup analysis showed adjuvant gemcitabine chemotherapy to be associated with an increased survival in PDAC patients, but this could be a cause rather than a result of receiving adjuvant treatment. Outcomes could be influenced by guarantee-time bias, as patients with a poor prognosis could be less likely to receive adjuvant chemotherapy, and patients might have passed away before the start of treatment. Nonetheless, adjuvant chemotherapy has been found to prolong disease-free and overall survival in patients who have undergone an operation for the treatment of PDAC.[60,61]

The main strengths of this series are its relatively large size due to the nationwide study design, the use of established definitions, and the use of multiple summarizing statistics to report 90-day complication rates. Finally, the survival data are reliable since they were obtained from the nationwide municipal personal records database.

The relatively good survival of patients with colon cancer as presented in this series supports the recommendation of current guidelines to perform a multivisceral en bloc resection for advanced colon cancer.[9,18,62] In contrast to PDAC, colon cancer is starting to become a chronic disease, partially due to expanding opportunities for curative operations, even in the case of metastasized tumors.[63-66] Therefore, the main challenge for the treatment of colon cancer is to prevent disease recurrence and to improve patients' quality of life.

In conclusion, this nationwide cohort of PD-colon found an acceptable 5-year cumulative survival in patients who underwent a radical (R0) resection for PDAC, suggesting that PD-colon was justified in a selected subset of patients. However, a considerably high postoperative complication rate was seen among all patients. Importantly, PD-colon appeared to be a valuable option for selected patients with colon cancer invading periampullary structures.

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