The American Journal of Surgery 220 (2020) 1235–1241

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Distal pancreatectomy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: Identifying risk and improving patient selection

Brianne J. Sullivan*, Natasha L. Leigh, Eliahu Y. Bekhor, Matthew Carpiniello, Daniel Solomon, Deepa R. Magge, Umut Sarpel, Benjamin J. Golas, Daniel M. Labow

Division of Surgical Oncology, Mount Sinai St. Luke's Roosevelt, USA

ARTICLE INFO

Article history:
Received 15 February 2020
Received in revised form
22 April 2020
Accepted 25 June 2020

Keywords:
Cytoreductive surgery
Peritoneal carcinomatosis
Distal pancreatectomy

ABSTRACT

Background: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has become a principal tool in the management of peritoneal carcinomatosis (PC), but inclusion of pancreatic resection to obtain optimal debulking remains controversial.
Methods: We performed a retrospective review of 419 patients with PC who underwent CRS/HIPEC. The patients were divided into two cohorts, those with distal pancreatectomy (DP) and those without (NP), and morbidity and survival outcomes were compared.
Results: The DP cohort (n = 37) and the NP cohort (n = 371) had similar clinicopathologic characteristics (age, $p = 0.596$; gender, $p = 0.328$; ASA, $p = 0.072$). Operative time, number of organs resected, and EBL were greater in the DP cohort (<0.0001). A complete cytoreduction was achieved in 90% of the NP cohort versus 69% of the DP cohort ($p = 0.0004$). Major perioperative morbidity was more common in those with pancreatic resection (41% vs 19%, $p = 0.002$). However, there was no significant difference in 90-day mortality or overall survival.
Conclusion: Achieving complete cytoreduction is critical to improving long term outcomes for patients with PC. Although pancreatic resections are associated with higher morbidity, short-term survival is not impacted adversely. Pancreatic involvement should not be a strict exclusion criterion for CRS/HIPEC, but patients need to be selected carefully, with close attention to disease burden prior to proceeding.

Background

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has become widely accepted as a treatment for carcinomatosis secondary to colorectal, appendiceal, pseudomyxoma peritonei, malignant peritoneal mesothelioma, and ovarian carcinomatosis.[1–6] However, the treatment is associated with noteworthy morbidity and mortality, with serious morbidity reported from 12% to 52%[7] and a mortality rate of 3.8% in one of the largest retrospective reviews.[8] Given the considerable morbidity and mortality, physicians are searching for criteria to guide patient selection.[9,10] Although careful patient selection is constantly recommended in the CRS/HIPEC literature, aside from inability to obtain a complete cytoreduction (i.e., eradicate all macroscopic disease with less than 2.5 mm of tumor implants), it is currently ill-defined as to what characteristics make a patient inoperable.

Multiple studies have consistently shown that complete cytoreduction (CCR) after CRS/HIPEC is one of the most important prognostic factors for progression free survival (PFS) and overall survival (OS).[1,11–13] Thus, inability to obtain a complete cytoreduction is accepted as a contraindication to proceeding with CRS/HIPEC other than for palliative intent. In order to obtain a complete cytoreduction, a pancreatic resection is often required when there is extensive disease in the left upper quadrant.[14] In patients at high risk for severe complications pancreatic resection during CRS/HIPEC has been considered a relative contraindication.[14] There is limited literature on the outcomes of distal pancreatectomy when combined with CRS/HIPEC. We sought to evaluate the morbidity and mortality of all patients who underwent CRS/HIPEC and distal pancreatectomy over a ten-year period at a high-volume center to

* Corresponding author. 425 West 59th St., 7th floor, New York, NY, 10019, USA.
E-mail address: brianne.sullivan@mountsinai.org (B.J. Sullivan).

https://doi.org/10.1016/j.amjsurg.2020.06.045
0002-9610/

better determine if the risks of surgery outweighs its potential benefits.

Methods

Following Institutional Review Board approval by the Mount Sinai School of Medicine, we performed a retrospective analysis of a prospectively maintained database of all patients with peritoneal carcinomatosis who underwent CRS/HIPEC from March 2007–June 2018. Patients were excluded from the study if their surgery was aborted. Patients were divided into two cohorts based upon whether or not a distal pancreatectomy was performed. The primary outcomes of the study were 30-day morbidity, 90-day mortality, and OS.

Surgical procedure

All CRS/HIPEC surgeries were performed in a standard fashion, as previously described by Tabrizien et al.[15] Diagnostic laparoscopy was performed in all cases. If the operating surgeon deemed there was minimal likelihood of achieving complete cytoreduction the surgery was aborted. The surgery was performed by one of six Mount Sinai faculty surgical oncologists who specialize in CRS/HIPEC. The Peritoneal Cancer Index (PCI) was calculated prior to debulking, with the goal to obtain a Completeness of Cytoreduction (CC) score of CC-0 or CC-1, defined as no macroscopic disease and residual tumor implants less than 2.5 mm respectively.[15,16] PCI was calculated based upon the extent of disease in each region of abdomen as described by Sugarbaker.[16]

The distal pancreas was resected for peritoneal surface disease and not for parenchymal disease. The technique for performing the distal pancreatectomy was consistent amongst all surgeons. If the pancreas was deemed to have resectable disease burden, then the pancreas was mobilized medially to expose the splenic vein and artery. The vein and artery were divided with a vascular stapler and the pancreatic body transected with a reinforced staple load. The remainder of the pancreatic body, tail, and spleen were mobilized in medial to lateral fashion. In all cases a drain was left in the left upper quadrant.

Cytoreduction involved resection of primary tumor following oncologic resection principles as well as resection or peritoneal stripping of any organ or parietal peritoneal surface grossly covered with tumor. Following cytoreduction, HIPEC was performed with the closed abdominal technique. Mitomycin C was the most common agent and was administered over two doses, 40 mg over 60 min and 10 mg over 30 min, for a total of 90 min of perfusion, with a target intraperitoneal temperature of 41–43 °C. Cisplatin or carboplatin were used in a few patients for gynecologic malignancy or mesothelioma.[15]

Data collection/outcomes

Clinicopathologic data collected on each patient included age, sex, American Society of Anesthesiologist (ASA) score and Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), pre-operative albumin and tumor markers, administration of neoadjuvant chemotherapy and primary origin of malignancy. Albumin was recorded as low if it was under 3.5 g/dl. Perioperative outcomes included PCI, number of organs resected, number of anastomoses, CC-score, HIPEC agent, estimated blood loss (EBL), operating time, and operating room (OR) transfusion. Diaphragm stripping/resection, peritonectomy, and omentectomy were counted towards the number of organs resected.

Postoperative outcomes evaluated were development of an ileus, use of parenteral nutrition, abscesses, enterocutaneous and pancreatic fistulas (PF), anastomotic leak, length of stay (LOS), intensive care unit (ICU) admission, 30-day morbidity (Clavien-Dindo score 1–2 = minor morbidity, Clavien-Dindo score 3–4 = severe morbidity), 90-day re-operation, and 90-day mortality.[17] Ileus was defined by an international consensus panel, consisting of two or more of the following on or after POD 4: nausea, vomiting, abdominal distention, inability to tolerate an oral diet, and radiologic confirmation.[18] Respiratory variables tracked consisted of pleural effusions, use of diuresis, and respiratory distress. Respiratory distress was defined as requiring oxygen supplementation for a clinical change in respiratory status, bilevel positive airway pressure (BiPAP), and intubation. Long term outcomes included use of adjuvant chemotherapy, OS, and PFS. Patients who did not have recurrence were censored to their last follow-up visit. Surveillance imaging and office notes were used to determine recurrence and if available the sites of recurrence were recorded. OS was calculated from the date of surgery to the date of death, and those who did not die were censored at their last follow-up visit. A subset analysis of the DP cohort was also performed comparing the suboptimally-cytoreduced DP patients versus the optimally-cytoreduced patients.

Statistical analysis

SAS® software, version 9.4, was used for all statistical analysis. Categorical variables were compared using Chi squared tests and reported as frequencies and percentages. Continuous variables were tested for normality with a Shapiro-Wilk test and found to be nonparametric, thus they were compared using a Wilcoxon rank sum test and reported as median values and interquartile ranges (IQR). OS and PFS were estimated using the Kaplan-Meier method and survival curves were calculated using the log-rank test. A multivariable logistic regression analysis was performed to determine independent risk factors for severe 30-day morbidity. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Four hundred and eight patients completed CRS/HIPEC for PC that met inclusion criteria. Thirty-seven patients underwent a distal pancreatectomy (DP) and the remaining 371 had no pancreatic resection (NP). Overall the cohorts had similar clinicopathologic characteristics (Table 1). The median age for all patients was 55 years old. Gender distribution was skewed towards more female (M:F, 157:251). Pre-op tumor markers did not vary significantly between cohorts. The distribution of ASA score between the cohorts approached significance, with greater co-morbidity in those who underwent a pancreatic resection (ASA IV 19% vs 7%, $p = 0.072$). ECOG status was similar between the cohorts ($p = 0.931$). Around 20–30% of each cohort underwent neoadjuvant chemotherapy prior to CRS/HIPEC and there was no significant difference between the cohorts in lymph node metastasis during pre-operative staging (NAC $p = 0.131$, lymph node metastasis $p = 0.275$).

The distribution of the primary origin of peritoneal carcinomatosis was statistically different. Twenty-two percent of patients in the DP cohort had an upper gastrointestinal origin versus 7% of the NP cohort ($p = 0.008$). The three most common primary malignancies for the DP cohort were appendiceal carcinoma (30%), low-grade appendiceal mucinous neoplasm (LAMN) (22%), and gastric cancer (22%). The NP cohort's most common primary malignancy was colorectal (31%), followed by LAMN (22%) and appendiceal carcinoma (20%).

Table 1
Clinicopathologic characteristics of patients with distal pancreatectomy vs without.

Characteristic	All patients (n = 408)	Distal pancreatectomy (n = 37)	No pancreatectomy (n = 371)	p-value
Age at surgery, years	55 (46–62)	54 (46–61)	55 (47–62)	0.673
Male Gender	157 (38–62)	17 (46)	140 (38)	0.328
ASA score				
II	69 (17)	4 (11)	65 (18)	0.072
III	305 (75)	26 (70)	279 (75)	
IV		7 (19)	26 (7)	
BMI	26 (22–29)	23 (21–28)	26 (22–29)	0.165
Low albumin	159 (39)	18 (48)	141 (38)	0.300
PC primary origin				
Upper gastrointestinal	35 (9)	8 (22)	27 (7)	0.008
Appendiceal	85 (20)	11 (30)	74 (20)	
Colorectal	119 (29)	4 (11)	115 (31)	
PMP	89 (22)	8 (22)	81 (22)	
Mesothelioma	22 (5)	3 (8)	19 (5)	
Ovarian	16 (4)	1 (3)	15 (4)	
Hepatobiliary	20 (5)	1 (3)	19 (5)	
Other	22 (5)	1 (3)	21 (6)	
Lymph node metastases	63 (15)	8 (22)	55 (15)	0.275
NAC	92 (23)	13 (32)	80 (22)	0.131

ASA American society of anesthesiologists, PC peritoneal carcinomatosis, PMP pseudomyxoma peritonei, NAC neoadjuvant chemotherapy.
Raw numbers followed by percentages in parenthesis for categorical variables. Median followed by interquartile ranges in parentheses for continuous variables.

Perioperative outcomes

The DP cohort had significantly more disease at the time of surgery as evidenced by higher PCI (18 vs 10, $p < 0.0001$) and an average of 8 organs resected compared to 3 in the NP cohort ($p < 0.0001$) (Table 2). Eight patients in the DP cohort underwent a total gastrectomy, compared to 10 in the NP cohort. Splenectomy was performed in all patients who had a distal pancreatectomy and 59 additional patients in the NP cohort. The surgeries in the DP cohort had longer operating times, higher EBL, and greater transfusion requirements (450 min vs 297 min; 1.0 L vs 0.2 L; 62% vs 10%, $p < 0.0001$). The HIPEC agent for the majority of patients in both cohorts was mitomycin C (DP: 85%, NP: 88%, $p = 0.679$). Carboplatin and cisplatin were administered in 8% and 3% of the patients, respectively. The ability to obtain a complete cytoreduction was much lower for the DP cohort. A CC-0/1 was achieved for 90% of the NP cohort but only 69% of those who required a distal pancreatectomy ($p = 0.0043$).

Table 2
Perioperative outcomes of patients with distal pancreatectomy vs without.

Value	All patients (n = 408)	Distal pancreatectomy (n = 37)	No pancreatectomy (n = 371)	p-value
PCI	10 (6–18)	18 (14–27)	10 (5–18)	<0.0001
Number of organs resected	3 (2–5)	8 (6–9)	3 (1–5)	<0.0001
Number of anastomoses				
0	201 (49)	11 (30)	190 (51)	0.043
1–2	181 (44)	23 (62)	158 (43)	
≥3	26 (6)	3 (8)	23 (6)	
CC score				
CC-0/1	347 (88)	25 (69)	322 (90)	0.0004
CC-2/3	48 (12)	11 (31)	37 (10)	
HIPEC agent				
Mitomycin C	359 (88)	32 (85)	327 (88)	0.679
Carboplatin	33 (8)	3 (8)	30 (8)	
Cisplatin	11 (3)	2 (5)	9 (2)	
EBL, cc	200 (100–500)	1000 (500–2000)	200 (100–500)	<0.0001
OR transfusion	99 (24)	23 (62)	37 (10)	<0.0001
OR time, mins	305 (246–393)	450 (379–508)	297 (244–368)	<0.0001
LOS, days	7 (5–10)	10.5 (8–17)	6 (5–9)	<0.0001
ICU admission	126 (31)	24 (67)	102 (27)	<0.0001
ICU LOS, days	0 (0–2)	2.5 (1–8)	0 (0–2)	0.029
Ileus	87 (25)	11 (35)	76 (24)	0.143
TPN	28 (8)	7 (21)	21 (6)	0.003
Anastomotic leak	33 (9)	7 (19)	26 (7)	0.011
Abscess	27 (6)	9 (24)	18 (5)	<0.0001
Enterocutaneous fistula	14 (3)	2 (5)	12 (3)	0.489
Respiratory distress	48 (12)	10 (27)	38 (10)	0.003
Pleural effusion	94 (26)	20 (57)	74 (23)	<0.0001
Renal failure	21 (6)	4 (11)	17 (5)	0.139
30-day severe morbidity	86 (21)	15 (41)	71 (19)	0.002
90-day mortality	14 (3)	1 (3)	13 (4)	0.799
90-day Re-operation	48 (11)	7 (19)	41 (11)	0.157

CRS cytoreductive surgery, HIPEC hyperthermic intraperitoneal chemotherapy, PCI peritoneal carcinomatosis index, CC complete cytoreduction, EBL estimated blood loss, OR operating room, LOS length of stay, ICU intensive care unit, TPN total parenteral nutrition, severe morbidity = Clavien-Dindo 3 or 4.
Raw numbers followed by percentages in parenthesis for categorical variables. Median followed by interquartile ranges in parentheses for continuous variables.

Postoperative outcomes

ICU admission was more prevalent in the DP cohort ($p < 0.0001$) and hospital length of stay was longer (10.5 vs 6, $p = 0.007$). No difference was seen in the rates of ileus ($p = 0.143$), yet the need for total parenteral nutrition (TPN) was higher in those with pancreatic resection (21% vs 6%, $p = 0.003$). Patients with pancreatic resection were not significantly more prone to acute renal failure ($p = 0.139$), but they were more likely to develop respiratory complications and pleural effusions (27% vs 10%, $p = 0.003$; 57% vs 23% $p < 0.0001$ respectively). Anastomotic leaks (19% vs 7%, $p = 0.011$) and abscesses (24% vs 5%, $p < 0.0001$) were more common in the DP cohort. There was no difference between the cohorts in the development of enterocutaneous or colovesicular fistulas ($p = 0.489$). Five patients (13.5%) with a distal pancreatectomy had a PF as defined by the International Study Group.[19] Of these patients, three required drainage by interventional radiology and two patients required a return to OR for anastomotic leaks. Two patients had high drain output and elevated amylase but no clinical symptoms and thus were classified as a biochemical leak.

Forty-one percent of those with pancreatic resection had a Clavien-Dindo score of 3 or 4, versus 19% of the NP cohort ($p = 0.002$). Yet, neither 90-day mortality nor 90-day reoperation was significantly different ($p = 0.799$, $p = 0.157$). Adjuvant chemotherapy was administered in close to 50% of each cohort. The mean follow-up time for all patients who underwent CRS/HIPC was 9.5 months. Progression-free survival was shorter for the DP cohort. At a one-year follow up, only 20% of the DP cohort remained free of disease, versus 53% of the NP cohort ($p < 0.0001$). In both cohorts peritoneal disease was the most common site of recurrence. Nonetheless, taking into account the short follow-up time the OS was not significantly different (Table 3, Fig. 1).

Multivariate analysis

A multivariate analysis was preformed to evaluate whether the excess morbidity in the DP cohort remained significant after controlling for PCI, upper GI pathology, cytoreductive score, and intraoperative transfusion (Table 4). After controlling for the above variables, pancreatic resection was not a significant predictor of severe 30-day morbidity. Intraoperative transfusion (OR 4.1, CI 2.2–7.5) was the only variable found to be positively correlated with severe 30-day morbidity.

Subset analysis

A comparison of those suboptimally-cytoreduced (SC) in the DP cohort versus optimally-cytoreduced (OC) was performed using the same variables as used in the DP versus NP cohorts. Eleven patients were classified as SC, the remaining 26 were in the OC group. We found no significant difference in patient characteristics. In terms of perioperative outcomes, intraoperative transfusions (91% vs 50%; SC vs OC, $p = 0.019$), PCI (28 vs 16; $p = 0.0006$), OR time (493 min vs 415 min, $p = 0.021$), and EBL (2.0 L vs 0.5 L, $p = 0.007$) were all greater in the SC group. PCI ranged from 25 to 32 in the SC group and 13–24 in the OC group. ICU length of stay, major 30-day morbidity, and 90-day mortality were not significantly different. A similar number of patients in each group underwent adjuvant chemotherapy. PFS was 0 for all patients in the SC cohort as these patients were never considered disease free. OS also did not differ significantly.

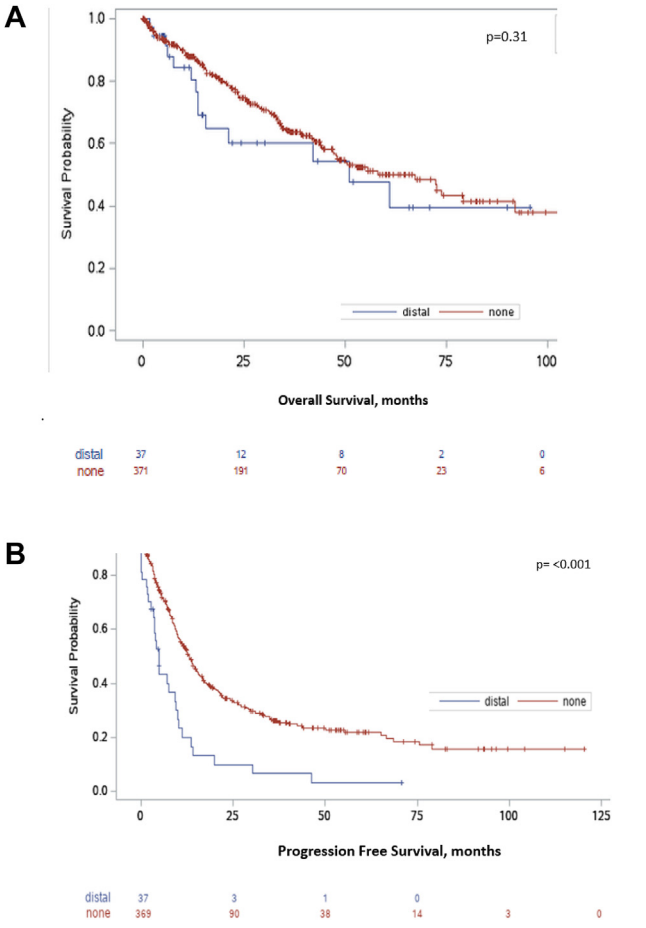

Fig. 1. a) Kaplan-Meyer survival curves for DP and NP cohorts, with number of patients alive from each cohort listed below. b) Kaplan-Meyer progression free survival curve for DP and NP cohorts, with number of patients recurrence free for each cohort listed below.

Table 3
Postoperative outcomes of patients with distal pancreatectomy vs without.

Value	All patients (n = 408)	Distal pancreatectomy (n = 37)	No pancreatectomy (n = 371)	*p*-value
Adjuvant chemotherapy	161 (46)	17 (51)	144 (45)	0.474
Follow-up time, months	9.5 (3.6–22.1)	4.1 (1.7–9.5)	10.5 (3.8–24.3)	0.0003
OS, % (number)				
1-year OS	87 (281)	77 (20)	88 (260)	0.310
3-year OS	63 (140)	54 (9)	64 (130)	
5-year OS	49 (46)	40 (5)	49 (31)	
PFS, % (number)				
1-year PFS	50 (173)	16 (5)	53 (165)	0.0004
3-year PFS	25 (58)	3 (1)	34 (93)	
5-year PFS	20 (19)	0 (0)	21 (18)	

OS overall survival, PFS progression-free survival.

Table 4
Multivariate analysis evaluating for variable associated with increased severe 30-day morbidity.

Variable	Odds ratio	Confidence Interval (95%)	p-value
Distal pancreatectomy	0.7	0.3–1.6	0.427
Intraoperative transfusion	4.1	2.2–7.5	<0.001
CC-score group	0.5	0.2–1.3	0.139
Upper GI primary pathology	2.2	0.9–5.0	0.062
PCI	1.0	0.9–1.1	0.117

CC complete cytoreduction, GI gastrointestinal, PCI peritoneal carcinomatosis index.

Discussion

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy emerged about 3 decades ago as a novel treatment that has been found to prolong survival in patients with disseminated peritoneal carcinomatosis secondary to epithelial malignancies.[20–23] Nonetheless, given the significant morbidity and mortality associated with extensive debulking and intraperitoneal chemotherapy appropriate patient selection is critical. As centers become more familiar with CRS/HIPEC and outcomes improve, researchers are seeking to refine the indications and contraindications for the surgery.[7,8,24] Research has focused on various primary malignancies with peritoneal carcinomatosis to determine which respond well and have a survival benefit. Randomized trials and large retrospective reviews have shown a survival advantage for colorectal, appendiceal, peritoneal mesothelioma, and ovarian primaries.[1,25–28] Although not yet accepted as standard of care, promising results have been seen for peritoneal carcinomatosis secondary to gastric cancer as well.[29] Additionally, studies attempt to elucidate which patient characteristics are associated with worse prognosis.[9,10,24] Currently some prognostic indicators found in multiple studies include performance status, institutional experience, completeness of cytoreductive surgery, extent of carcinomatosis, and origin of PC.[8,22]

There has been limited investigation of distal pancreatectomy and CRS/HIPEC. Our findings align with largest previous study, demonstrating that DP during CRS/HIPEC results in a significant increase in major perioperative morbidity but not in overall mortality.[30] Doud et al. reviewed over 1000 patients who underwent CRS/HIPEC and found 63 required a distal pancreatectomy. The primary focus of the paper was the impact of DP on outcomes. The 90-day mortality for the DP cohort was 4.8% ($n = 3$) and was not significantly different from those without pancreatic resection. OS was only evaluated for patients with appendiceal primary malignancies, and also was not significantly different. The distribution of primary malignancy was slightly different from our findings, with appendiceal being the most common primary malignancy for both cohorts and upper GI/gastric malignancies were not specified. As with our study, Doud et al. performed a multivariate analysis and found DP was not a significant predictor of 30-day major morbidity after controlling for age, R resection status, and number of organs resected. Our study adds to the small volume of existing data and demonstrates similar findings to Doud, but in a more diverse population with varying primary pathologies.

Distal pancreatectomy in itself is a relatively morbid procedure, with PF being one of the most harmful and relevant complications.[19] Retrospective studies report overall rates of PF between 23 and 31% and grade B/C fistulas between 10 and 15%.[14,31] The definition of PF was redefined in 2016 by the International Study Group of Pancreatic Fistula to include clinically relevant symptoms in the presence of drain output and drain amylase greater than 3× the normal serum level. The prior grade A fistula is now referred to as a biochemical leak since it has been found to not have clinical importance. The updated definition is an attempt to reduce inconsistencies in the grading system for postoperative pancreatic fistulas which has made evaluation of operative outcomes challenging.[19]

A study compared the severity of PF after distal pancreatectomy with CRS/HIPEC to after pancreatectomy alone, and found an equal incidence of fistulas between the two groups. Although the fistulas in the HIPEC group were more severe, there was no increased risk of other postoperative complications and no impact on survival.[21] An international multicenter review examined outcomes of 118 patients with peritoneal surface malignancy who underwent CRS/HIPEC with distal pancreatectomy and analyzed the incidence, clinical impact and risk factors for PF development. The 30-day and 90-day mortality rates were 5.9% and 7.6% respectively and severe morbidity was 44%. In this study patients who developed a PF had higher rates of severe complications, but not higher mortality compared to those with DP who did not develop a PF. Specifically, patients who developed a PF had higher rates of intra-abdominal collections and associated sepsis but pulmonary, cardiovascular, renal, and hematologic complications were similar between those who developed a PF and those who did not. On multivariate analysis, PCI over 20 and operative time over 550 min were independently associated with PF.[14]

In our DP cohort, 13.5% developed a PF, two patients required IR drainage and one required return to the OR for an anastomotic leak. We did see significantly higher rates of anastomotic leaks in our DP cohort, however 90-day reoperation was no different. It is not surprising the DP cohort would have higher anastomotic leak rates given our DP patients had higher disease burden, more organs resected, and more anastomoses. Seventy percent of the DP cohort had 1 or more anastomoses versus 49% of the NP cohort. In a single institution retrospective review of over 1000 patients, prognostic factors and significance of gastrointestinal leak after CRS/HIPEC on multivariate analysis found ECOG performance status and number of anastomoses to be predictors of leak.[32]

One postoperative characteristic we wanted to explore was if the higher morbidity associated with distal pancreatectomies impacted the patients' ability to complete adjuvant chemotherapy. Although we did not have the date chemotherapy was initiated after surgery to determine if there was a delay in adjuvant treatment, the number of patients to undergo adjuvant chemotherapy was the same in each cohort. The fact the mortality was not significantly different between the cohorts suggests the higher morbidity associated with DP does not have a clinically significant impact on the timing and completion of adjuvant chemotherapy. This is concurrent with a recent randomized trial published by Van Driel et al. looking at patients with stage III ovarian cancer who either underwent CRS/HIPEC versus just CRS and found the addition of HIPEC did not result in a delay or reduced completion of postoperative chemotherapy.[26] However, a definitive conclusion cannot be drawn from our data regarding how the increased morbidity in the DP cohort affected the timing and completion of adjuvant therapy given the small sample size and their mixed tumor types, which likely makes the association between adjuvant therapy and survival less clear.

In a prospective study of 30 patients, an attempt was made to define predictive factors for successful CRS/HIPEC in colorectal cancer. Malignant ascites, PCI>20, and rectal origin were poor prognostic factors that were associated with a failure to achieve a CC 0/1 surgery and consequently poor survival.[24] Verwaal et al. randomized control trial also showed rectal origin carrying poorer outcomes though other studies have shown rectal origin to have no impact.[33,34] Likewise, some institutions will not operate on patients with PCI above a certain level, yet patients have been reported to have long-term survival with PCIs over 20.[35] In our subset analysis

of our DP cohort comparing SC to OC the PCI ranged from 25 to 32 in the SC group, and 13 to 24 in the OC group. Clearly, in a heterogenous entity such as peritoneal carcinomatosis it can be difficult to draw conclusions regarding what patient characteristics and clinical scenarios produce optimal outcomes. Hence, it is important to continue to gather and analyze data, in an effort to create the best evidence-based practice.

Our data was collected over a 10-year time frame. Out of the 37 patients that underwent a distal pancreatectomy 18 patients had the operation during the first five years while 19 had the operation during the latter years. Our institution studied our 10-year experience and not unsurprisingly found that outcomes were better in terms of longer survival and PFS in the latter cohort.[36] The late cohort had lower PCI (10 vs 16) and had similar CC 0/1 scores with less organs resected, shorter operations, lower EBL and more procedures were aborted. As a whole, increased experience translated into improved perioperative and oncologic outcomes over a 10-year period. We do not think this gradual improvement significantly impacts our study results as patients selected for a distal pancreatectomy were almost equally distributed over the early and late years and no specific changes took place in terms of how our operating surgeons approached or performed a distal pancreatomy.

This study was limited by its retrospective nature, heterogeneous primary pathology, the small number of patients in our distal pancreatomy cohort, and the relatively short median follow-up time.

Conclusion

A review of all patients who underwent CRS with distal pancreatectomy and HIPEC at a high-volume institution demonstrated that these patients have increased morbidity but no increase in short-term mortality compared to patients that underwent CRS and HIPEC without a distal pancreatectomy. Patients in our DP cohort were less likely to achieve a CC0/1 resection. Incomplete cytoreduction equates to shorter PFS, and likely with a longer follow-up time, it translates into shorter OS. Therefore, the extent of disease must be very carefully evaluated before proceeding with a distal pancreatectomy and the surgery should be aborted once it becomes clear a CC0/1 reduction cannot be achieved. Any patients with PCI > 25 in our distal pancreatectomy cohort were unable to be completely cytoreduced. The highest PCI in our DP cohort that achieved a CC0/1 reduction was 24. Although calculating PCI is not an exact measure, we would advise once a PCI approaches or exceeds 25 the surgeon should re-consider proceeding with a distal pancreatectomy. Meta-analyses of patients with CRS/HIPEC and distal pancreatectomy could help elucidate if the increased morbidity is worth the risk in an effort to prolong survival. From our single institution experience we would continue to advocate that pancreatic involvement does not indicate unresectable disease. Nonetheless, patients must be approached with caution and with an understanding that the chances of obtaining a complete cytoreduction are lower, and therefore it is critical to carefully assess tumor burden.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We have no acknowledgements of any outside support for this paper.

References

1. Kuncewitch M, Levine E, Shen P, Votanopoulos KI. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for appendiceal tumors and colorectal adenocarcinomas. *Clin Colon Rectal Surg*. 2018;31:288–294. https://doi.org/10.1055/s-0038-1642052, 05.
2. Sugarbaker PH. Peritoneal metastases, a Frontier for progress. *Surg Oncol Clin North Am*. 2018;27(3):413–424. https://doi.org/10.1016/j.soc.2018.02.001.
3. Newton AD, Bartlett EK, Karakousis GC. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a review of factors contributing to morbidity and mortality. *J Gastrointest Oncol*. 2016;7(1):99–111. https://doi.org/10.3978/j.issn.2078-6891.2015.100.
4. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol*. 2003;21(20):3737–3743.
5. Huo YR, Richards A, Liauw W, Morris DL. Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2015;41(12):1578–1589. https://doi.org/10.1016/j.ejso.2015.08.172.
6. Sugarbaker PH. Update on the management of malignant peritoneal mesothelioma. *Transl Lung Cancer Res*. 2018;7(5):599–608. https://doi.org/10.21037/tlcr.2018.08.03.
7. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. *Ann Surg*. 2009;249(6):900–907. https://doi.org/10.1097/SLA.0b013e3181a45d86.
8. Levine EA, Stewart 4th JH, Shen P, Russell GB, Loggie BL, Votanopoulos KI. Cytoreductive surgery and hyerthermic intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. *J Am Coll Surg*. 2014;218(4):573–585. https://doi.org/10.1016/j.jamcollsurg.2013.12.013.
9. Rivard JD, McConnell YJ, Temple WJ, Mack LA. Cytoreduction and heated intraperitoneal chemotherapy for colorectal cancer: are we excluding patients who may benefit? *J Surg Oncol*. 2014;109(2):104–109. https://doi.org/10.1002/jso.23446.
10. Baratti D, Kusamura S, Mingrone E, Balestra MR, Laterza B, Deraco M. Identification of a subgroup of patients at highest risk for complications after surgical cytoreduction and hyperthermic intraperitoneal chemotherapy. *Ann Surg*. 2012;256(2):334–341. https://doi.org/10.1097/SLA.0b013e31825704e3.
11. Shen P, Levine EA, Hall J, et al. Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. *Arch Surg*. 2003;138(1):26–33. https://doi.org/10.1097/SLA.0b013e31825704e3.
12. Votanopoulos KI, Bartlett D, Moran B, et al. PCI is not predictive of survival after complete CRS/HIPEC in peritoneal dissemination from high-grade Appendiceal primaries. *Ann Surg Oncol*. 2018;25(3):674–678. https://doi.org/10.1245/s10434-017-6315-3.
13. Van Sweringen HL, Hanseman DJ, Ahmad SA, Edwards MJ, Sussman JJ. Predictors of survival in patients with high-grade peritoneal metastases undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Surgery*. 2011;152(4):617–624. https://doi.org/10.1016/j.surg.2012.07.027.
14. Schwarz L, Votanopoulos K, Morris D, et al. Is the combination of distal pancreatectomy and cytoreductive surgery with HIPEC reasonable?: results of an international multicenter study. *Ann Surg*. 2016;263(2):369–375. https://doi.org/10.1097/SLA.0000000000001225.
15. Tabrizian P, Shrager B, Jibara G, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. *J Gastrointest Surg*. 2014;18(5):1024–1031. https://doi.org/10.1007/s11605-014-2477-5.
16. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH, ed. *Peritoneal Carcinomatosis: Principles of Management Kluwer*. Boston, USA: Academic Publishers; 1996, 359-357.
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
18. Vather RTS, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. *J Gastrointest Surg*. 2013;17(5):962–972.
19. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Sugery*. 2017;161(3):584–591. https://doi.org/10.1016/j.surg.2016.11.014.
20. Sugarbaker PH. Surgical treatment of peritoneal carcinomatosis: 1988 Du Pont lecture. *Can J Surg*. 1989;32(3):164–170.
21. Downs-Canner S, Ding Y, Magge DR, et al. A comparative analysis of postoperative pancreatic fistulas after surgery with and without hyperthermic intraperitoneal chemoperfusion. *Ann Surg Oncol*. 2015;22(5):1651–1657. https://doi.org/10.1245/s10434-014-4186-4.
22. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer*. 2010;116(24):5608–5618. https://doi.org/10.1002/cncr.25356.

23. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004;15(22):3284–3292.
24. Mahmoud AM, Ismail YM, Hussien A, et al. Peritoneal carcinomatosis in colorectal cancer: defining predictive factors for successful cytoreductive surgery and hyperthermic intraperitoneal chemotherapy - a pilot study. *J Egypt Natl Canc Inst*. 2018;30(4):143–150. https://doi.org/10.1016/j.jnci.2018.10.004.
25. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*. 2008;15(9):2426–2432. https://doi.org/10.1245/s10434-008-9966-2.
26. van Driel WJ, Koole SN, Sonke GS. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med*. 2018;378(14):1363–1364. https://doi.org/10.1056/NEJMc1802033.
27. Spiliotis J, Halkia E, Lianos E, et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. *Ann Surg Oncol*. 2015;22(5):1570–1575. https://doi.org/10.1245/s10434-014-4157-9.
28. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol*. 2009;27(36):6237–6242. https://doi.org/10.1200/JCO.2009.23.9640.
29. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer*. 2017;79:1–14. https://doi.org/10.1016/j.ejca.2017.03.030.
30. Doud AN, Randle RW, Clark CJ, et al. Impact of distal pancreatectomy on outcomes of peritoneal surface disease treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2015;22(5):1645–1650. https://doi.org/10.1245/s10434-014-3976-z.
31. Tieftrunk E, Demir IE, Schorn S, et al. Pancreatic stump closure techniques and pancreatic fistula formation after distal pancreatectomy: meta-analysis and single-center experience. *PLoS One*. 2018;13(6). https://doi.org/10.1371/journal.pone.0197553.
32. Chouliaras K, Levine EA, Fino N, Shen P, Votanopoulos KI. Prognostic factors and significance of gastrointestinal leak after cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC). *Ann Surg Oncol*. 2017;24(4):890–897. https://doi.org/10.1245/s10434-016-5738-6.
33. Carmignani CP, Ortega-Perez G, Sugarbaker PH. The management of synchronous peritoneal carcinomatosis and hematogenous metastasis from colorectal cancer. *Eur J Surg Oncol*. 2004;30:391–398.
34. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004;15(22):16.
35. Cashin PH, Dranichnikov F, Mahteme H. Cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy treatment of colorectal peritoneal metastases: cohort analysis of high volume disease and cure rate. *J Surg Oncol*. 2014;110(2):203–206. https://doi.org/10.1002/jso.23610.
36. Leigh NL, Solomon D, Reingold D, et al. Improved survival with experience: a 10-year learning curve in hyperthermic intraperitoneal chemotherapy and cytoreductive surgery. *Ann Surg Oncol*. 2020;27:222–231.