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ORIGINAL ARTICLE

Utilization of Parenteral Nutrition Following Pancreaticoduodenectomy: Is Routine Jejunostomy Tube Placement Warranted?

Irina Yermilov · Sushma Jain · Evan Sekeris · David J. Bentrem · Oscar J. Hines · Howard A. Reber · Clifford Y. Ko · James S. Tomlinson

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Abstract *Introduction* Complications following pancreaticoduodenectomy (PD) often necessitate nutritional support. This study analyzes the utilization of parenteral nutrition (TPN) during the surgical admission as evidence for or against routine jejunostomy placement. *Methods* The California Cancer Registry (1994–2003) was linked to the California Inpatient File; PD for adenocarcinoma was performed in 1,873 patients. TPN use and enterostomy tube placement were determined and preoperative characteristics predictive of TPN use during the surgical admission were identified. *Results* Fourteen percent of patients received TPN, 23% underwent enterostomy tube placement, and 63% received no supplemental nutritional support. TPN was associated with longer hospital stay (18 vs. 13 days, $P < 0.0001$). The Charlson Comorbidity Index (CCI) ≥ 3 had nearly two-fold greater odds of receiving TPN (odds ratio [OR] = 1.85, $P < 0.005$). *Conclusion* Approximately 1 in 6 patients undergoing PD received TPN, which was associated with prolonged hospital stay. CCI ≥ 3 was associated with increased odds of TPN utilization. Selected jejunostomy placement in patients with high CCI is worthy of consideration.

Keywords Pancreaticoduodenectomy · Parenteral nutrition · Enterostomy tube · Postoperative nutrition

I. Yermilov · C. Y. Ko · J. S. Tomlinson (✉)
Department of Surgery, VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd., Los Angeles, CA 90073, USA
e-mail: James.Tomlinson@va.gov

I. Yermilov · S. Jain · E. Sekeris · O. J. Hines · H. A. Reber · C. Y. Ko · J. S. Tomlinson
Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

D. J. Bentrem
Department of Surgery, Northwestern University, Chicago, IL, USA

O. J. Hines · H. A. Reber · J. S. Tomlinson
Center for Pancreatic Disease, University of California, Los Angeles, Los Angeles, CA, USA

Introduction

Pancreaticoduodenectomy (PD) is a particularly morbid operation, with up to 48% of patients suffering a postoperative complication. The most common of these include delayed gastric emptying and pancreatic fistula, accounting for up to 30% of postoperative complications [1–7]. Many patients who suffer these complications require nutritional support in the postoperative period.

It is well accepted that surgical outcomes are linked to nutritional status. In a landmark VA cooperative study, Gibbs et al. demonstrated that preoperative albumin of less than 2.1 g/dl is associated with 29% postoperative mortality and 65% 30-day morbidity [8]. Furthermore, Neumeyer et al. determined that early and sufficient postoperative nutrition with either parenteral or enteral nutrition in general surgery patients resulted in both a shorter length of stay and reduced costs [9].

Although both enteral and parenteral nutrition are beneficial, enteral nutrition is the preferred route of delivery for many reasons. Enteral nutrition has been shown to have immuno-protective effects, including the stimulation of gut-associated lymphoid tissue and the synthesis and local release of immunoglobulin A. Furthermore, enteral nutrition stimulates gut motility and mucus production while reducing bacterial load, virulence, and adherence to the mucosa [10]. Additionally, enteral nutrition is associated with a four-fold decrease in cost when compared to parenteral nutrition [11]. In a multi-center randomized study comparing enteral to parenteral nutrition in malnourished gastrointestinal cancer patients, enteral nutrition was found to be associated with fewer postoperative complications and a reduced length of stay [12]. Complications commonly associated with parenteral nutrition include catheter sepsis, venous thrombosis, hepatic steatosis, and cholestasis [13].

Given the potential need for postoperative nutritional support after PD for adenocarcinoma and the relative benefits of enteral nutrition over parenteral nutrition, consideration of feeding jejunostomy at the time of resection may be indicated. There is no consensus regarding which patients, if any at all, should undergo jejunostomy tube placement at the time of PD. The goals of this study are: (1) to determine the utilization of parenteral nutrition following PD for pancreas cancer; (2) to predict those patients who will receive parenteral nutrition during the surgical admission; and (3) to determine whether there is evidence to support the routine placement of jejunostomy at the time of PD.

Methods

All patients with a diagnosis of pancreatic cancer recorded between the years of 1994 and 2004 in the California Office of Statewide Health Planning and Development (OSHPD) database were analyzed. These cases were linked to the California Cancer Registry database. The diagnosis was based on primary tumor site location (i.e., pancreas) and the ICD-9 procedure code for PD (52.51, 52.53, and 52.7). Only patients with adenocarcinoma were included; adenocarcinoma cases were selected using histopathology codes for adenocarcinomas, as defined by the International Classification of Diseases for Oncology, 3rd edition: 8000, 8001, 8003, 8010, 8012, 8020, 8021, 8022, 8030, 8031, 8033, 8035, 8041, 8045, 8046, 8050, 8070, 8140, 8141, 8144, 8154, 8201, 8210, 8230, 8260, 8290, 8310, 8440, 8441, 8450, 8452, 8453, 8460, 8470, 8471, 8472, 8473, 8480, 8481, 8482, 8490, 8500, 8501, 8503, 8550, 8560. Finally, 227 patients were excluded from the analysis due to miscoding or incomplete staging information; in order to ensure that all patients, in fact, underwent PD, only patients with documented regional lymph node excision and tumor size were included in the analysis.

The OSHPD database collects semi-annual data from all inpatients discharged from nonfederal hospitals licensed by the state of California. Each record includes patient demographics, hospital identification code, dates of admission and discharge, and codes for inpatient procedures and diagnoses. All procedures and diagnoses are categorized by the International Classification of Disease, 9th Clinical Modification (ICD-9, CM) coding scheme [14].

The OSHPD database has been linked to the California Cancer Registry for this study. The California Cancer Registry is a statewide population-based cancer surveillance system that records demographics, cancer type, extent of disease, and treatment data, along with survival information [15].

Patients who underwent PD for adenocarcinoma of the pancreas were then separated into three cohorts dependent upon nutritional support: (1) neither received parenteral nutrition nor underwent enterostomy tube placement; (2) received parenteral nutrition (ICD-9: 99.15); and (3) underwent enterostomy tube placement (ICD-9: 46.39). There were 56 patients who had received parenteral nutrition and had undergone enterostomy tube placement; these patients were excluded from further analysis. The cohort of patients that neither received parenteral nutrition nor underwent enterostomy tube placement were used as the reference cohort for analytic comparisons and is referred to as such in the text.

The demographics recorded for each patient included: age at diagnosis, gender, race/ethnicity, *T*-stage, and nodal status. The Charlson Comorbidity Index (CCI) was utilized to risk-adjust patients according to their comorbidities. The CCI consists of 19 disease conditions with different weights based on risk of mortality within one year. For example, myocardial infarction carries a score of 1, whereas severe liver disease carries a score of 3. These scores are summed for each patient, indicating a higher burden of comorbid disease with an associated increased risk of one-year mortality [16]. In this study, a modified CCI was recorded as 0, 1, 2, or 3 or more, excluding scoring for a cancer diagnoses, since all of the patients in this study had pancreatic cancer. In addition to the CCI, the presence of preoperative diabetes was analyzed. Using OSHPD data, analysis of the length of stay of the surgical admission, number of re-admissions, and perioperative mortality was performed. Overall survival in months was calculated from the date of operation to the date of death or last follow-up.

Statistical Analyses: Predicting the Receipt of TPN, Survival, and the Receipt of an Enterostomy Tube

t-test analyses of both means and proportions were completed, comparing the group that neither received parenteral nutrition nor underwent enterostomy tube placement to the parenteral nutrition and enterostomy tube groups. The Mann-Whitney test was utilized for the comparison of median values. *P*-values <0.05 were considered to be statistically significant. Survival analysis was performed using the Kaplan-Meier method and comparison was carried out using log-rank analysis. Multivariate logistic regression was performed to identify the preoperative predictors of the receipt of parenteral nutrition and the placement of enterostomy tube during the surgical admission, controlling for age, gender, nodal status, tumor size, and the CCI score. Additionally, mortality was analyzed utilizing multivariate logistic regression. Age, gender, nodal status, tumor size, the CCI score, parenteral nutrition, and enterostomy tube placement were covariates in the model. All statistical analyses were completed using Stata version 9.0 (Stata Corporation, College Station, TX).

Results

Univariate Analysis

In California, 1,873 patients were identified who underwent PD for pancreas cancer from 1994 to 2004. Administrative data for the surgical admission was analyzed, revealing that 262 patients received parenteral nutrition and 438 patients had an enterostomy tube placed, and 1,173 patients neither received parenteral nutrition nor underwent enterostomy tube placement. Approximately 83% of the patients were followed until death, and the median follow-up for survivors was 42.3 months. Comparative demographics of these three cohorts are shown in Table 1. The CCI differed significantly between the groups; proportionally more patients who received parenteral nutrition had a CCI ≥ 3 when compared to the group that received neither parenteral nutrition nor enterostomy tube placement (12.2% vs. 6.7%, $P < 0.003$). A CCI score of 1 was noted less often in the enterostomy tube group (20.8% vs. 28.9%, $P < 0.001$) than in the reference cohort, i.e., patients who did not undergo nutritional support intervention. In addition, there were less patients in the enterostomy tube group with T1 stage disease (17.6% vs. 23.1%, $P < 0.02$) and more with T3 stage disease (65.3% vs. 58.7%, $P < 0.02$). The prevalence of diabetes mellitus was separated from the CCI and independently analyzed; there was no difference in diabetes mellitus rates between groups.

Both the parenteral nutrition (18.0 vs. 13.0 days, $P < 0.0001$) and enterostomy tube (14 vs. 13 days, $P < 0.0007$) groups had increased median length of stay as compared to the reference cohort (Table 2). Interestingly, there was no difference in the number of readmissions among the groups. Furthermore, there was no difference in the perioperative survival. A small, yet significant reduction in the long-term survival was demonstrated in the parenteral nutrition group (median survival: 13.3 vs. 15.8 months, $P < 0.05$, $\chi^2 = 3.80$) compared to the reference cohort, i.e., patients who did not receive parenteral

Table 1 Demographics and comorbidities

Variable	No parenteral nutrition/ No enterostomy, $n = 1{,}173$	Parenteral nutrition, $n = 262$	Enterostomy, $n = 438$
Age: mean (SD)	64.5 (11.0)	65.3 (11.7)	65.1 (11.0)
Males (%)	51.2	52.3	51.6
Race (%)			
White	73.3	72.9	74.7
Black	5.9	3.8	5.5
Hispanic	14.1	13.0	13.2
Asian	6.5	10.3*	6.6
Other	0.3	0	0
Charlson score (%)			
0	56.0	52.7	60.3
1	28.9	25.2	20.8**
2	8.4	9.9	10.5
3+	6.7	12.2**	8.5
Diabetes (%)	23.6	24.4	20.6
T-stage (%)			
1	23.1	21.4	17.6*
2	4.9	5.0	3.7
3	58.7	61.1	65.3*
4	13.2	12.6	13.5
Node-positive (%)	55.2	57.6	59.8

* *P*-value < 0.03 compared to the "No parenteral nutrition/no enterostomy tube" group

** *P*-value < 0.003 compared to the "No parenteral nutrition/no enterostomy tube" group

Table 2 Survival and characteristics of surgical admission

Variable	No parenteral nutrition/ No enterostomy, $n = 1{,}173$	Parenteral nutrition, $n = 262$	Enterostomy, $n = 438$
Length of stay (days)			
Median	13	18*	14*
Mean (SD)	16.4 (10.8)	22.5 (16.6)**	18.7 (12.5)**
Number of readmissions			
Median	1	1	1
Mean (SD)	2.0 (2.3)	1.9 (2.1)	2.0 (2.1)
30-day mortality (%)	6.2	5.7	5.9
Overall survival			
Median	15.8	13.3**	15.6
Mean (SD)	22.9 (23.2)	21.3 (23.9)	23.3 (24.2)

* *P*-value < 0.0007 compared to the "No parenteral nutrition/no enterostomy tube" group

** *P*-value < 0.051 compared to the "No parenteral nutrition/no enterostomy tube" group

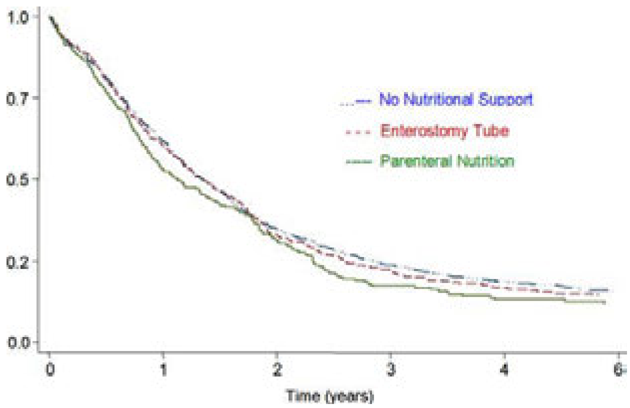

Fig. 1 Kaplan-Meier overall survival curves: parenteral, enterostomy tube, and no parenteral nutrition/no enterostomy tube groups

nutrition and did not undergo enterostomy tube placement (Fig. 1). Of note, there was no difference in either the perioperative or long-term survival in patients who had an enterostomy tube placed compared with the reference cohort (median survival: 15.6 vs. 15.8 months, $P < 0.63$, $\chi^2 = 0.23$).

Multivariate Analysis: Preoperative Characteristics Predictive of Parenteral Nutrition and Enterostomy Tube Placement

The entire cohort of patients was analyzed via multivariate logistic regression in order to predict pre-operative factors that predisposed to the utilization of parenteral nutrition (Table 3). Patients with a CCI score ≥3 had higher odds of receiving parenteral nutrition (odds ratio [OR] = 1.84, 95% confidence interval [CI]: 1.20–2.85; $P < 0.006$). Interestingly, neither age nor diabetes, which was analyzed in a model that did not include the CCI score, was predictive for the receipt of parenteral nutrition (data not shown).

Table 3 Prediction of parenteral nutrition ($n = 1{,}873$)

Covariate	Odds ratio	95% Confidence interval	*P*-value
Age	1.00	0.99, 1.02	0.45
Female	1.00		
Male	0.97	0.75, 1.26	0.82
Node-negative	1.00	–	–
Node-positive	1.06	0.80, 1.39	0.70
T1	1.00	–	–
T2	1.11	0.58, 2.15	0.75
T3	1.00	0.72, 1.40	0.99
T4	0.96	0.60, 1.54	0.88
Charlson 0	1.00	–	–
Charlson 1	1.01	0.73, 1.39	0.95
Charlson 2	1.18	0.75, 1.86	0.48
Charlson ≥3	1.84	1.19, 2.83	0.006

Table 4 Predictors of enterostomy tube placement ($n = 1{,}873$)

Covariate	Odds ratio	95% Confidence interval	*P*-value
Age	1.00	0.99, 1.01	0.33
Female	1.00	–	–
Male	1.00	0.80, 1.24	0.98
Node-negative	1.00	–	–
Node-positive	1.12	0.89, 1.40	0.33
T1	1.00	–	–
T2	1.00	0.55, 1.82	1.00
T3	1.40	1.05 1.87	0.02
T4	1.34	0.91, 1.98	0.14
Charlson 0	1.00	–	–
Charlson 1	0.67	0.51, 0.87	0.003
Charlson 2	1.11	0.77, 1.60	0.58
Charlson ≥3	1.00	0.67, 1.48	0.98

Multivariate analysis was also performed in order to determine predictors of enterostomy tube placement. When controlling for age, gender, race, tumor stage, node status, and CCI score, T3 disease (OR = 1.40, CI: 1.05, 1.87; $P < 0.02$) was found to be independently predictive of enterostomy tube placement, while a CCI score of 1 was predictive against enterostomy tube placement (OR = 0.67, CI: 0.51, 0.88; $P < 0003$) (Table 4).

Multivariate Analysis: Predictors of Mortality

The multivariate logistic regression model utilized to identify predictors of mortality for the entire cohort demonstrated age (OR = 1.02, CI: 1.01, 1.03; $P < 0.001$), node-positive status (OR = 2.57, CI: 1.99, 3.33; $P < 0.0001$), T3 stage (OR = 1.43, CI = 1.07, 1.91; $P < 0.02$), T4 stage (OR = 2.77, CI: 1.67, 4.59; $P < 0.0001$), CCI score of 2 (OR = 1.74, CI: 1.06, 2.85; $P < 0.02$), and CCI score ≥3(OR = 1.98, CI: 1.12, 3.50; $P < 0.02$) to be independent predictors of mortality. Parenteral nutrition trended towards significance (OR = 1.43, CI: 0.95, 2.13; $P < 0.08$); however, it was not found to be an independent predictor of mortality (Table 5).

There was an inverse relationship regarding the number of cases performed at a particular hospital and the percentage of those same patients who received parenteral nutritional support during their surgical admission. The top quartile of hospitals, with respect to the total number of cases performed, utilized parenteral nutrition in 12% of the patients, whereas the remaining quartiles utilized parenteral nutrition 19% of the time. Utilizing a *t*-test, this was found to be statistically significant, with a *P*-value equal to 0.005.

Table 5 Predictors of mortality ($n = 1,873$)

Covariate	Odds ratio	95% Confidence interval	*P*-value
Age	1.02	1.01, 1.03	0.001
Female	1.00	–	–
Male	0.95	0.74, 1.21	0.66
Node-negative	1.00	–	–
Node-positive	2.57	1.99, 3.33	<0.0001
T1	1.00	–	–
T2	0.89	0.52, 1.52	0.66
T3	1.43	1.07, 1.91	0.02
T4	2.77	1.67, 4.59	<0.0001
Charlson 0	1.00	–	–
Charlson 1	1.13	0.84, 1.52	0.41
Charlson 2	1.74	1.06, 2.85	0.03
Charlson ≥3	1.98	1.12, 3.50	0.02
Parenteral nutrition	1.43	0.95, 2.13	0.08
Enterostomy tube	1.08	0.79, 1.46	0.63

Discussion

Given the significant morbidity following PD and the malnutrition associated with the diagnosis of adenocarcinoma of the pancreas, many patients require perioperative nutritional support. Studies have demonstrated the benefits of enteral over parenteral nutrition. However, there is no consensus on jejunostomy tube placement following PD. The goal of this study was to analyze all patients who underwent PD for exocrine cancer of the pancreas in California over a 10-year period to determine whether there is evidence to support routine jejunostomy placement at the time of PD. Taking into account the known benefits of enteral over parenteral nutrition, our hypothesis was that the routine placement of enterostomy tube at the time of surgery would be indicated if a significant proportion of patients were receiving parenteral nutrition following PD.

The utilization of parenteral nutrition in the perioperative period has not been shown to improve mortality in non-malnourished patients [17]. Sandström et al. investigated patients undergoing various surgical procedures for both benign and malignant disease who received parenteral nutrition versus intravenous dextrose. Their results demonstrated no difference in mortality; however, the patients in the parenteral nutrition group suffered significantly more septic complications [18]. In fact, routine parenteral nutrition following pancreatic resection for pancreas cancer was evaluated in a randomized controlled trial performed at the Memorial Sloan-Kettering Cancer Center by Brennan et al. The results from this trial demonstrated no benefit for patients who received postoperative parenteral nutrition versus patients who did not receive parenteral nutritional support. Furthermore, increased complications, specifically, intra-abdominal infections, were seen in the parenteral nutrition group [19]. Given that routine postoperative parenteral nutrition following PD was not supported by the evidence, we asked whether or not routine jejunostomy placement was in the patient's best interest.

Considering the potential need for postoperative nutritional support and the fact that parenteral nutrition is associated with increased morbidity, as demonstrated in a randomized controlled trial by Brennan et al., our study was designed to determine the percentage of patients who received parenteral nutrition following PD for pancreas cancer and to determine if there is evidence to support the routine placement of a feeding enterostomy tube at the time of PD. In our search for evidence, patients were separated into three cohorts; patients that received parenteral nutrition during their surgical admission, patients that had an enteral tube placed within the same admission as their PD, and a reference cohort that had neither received parenteral nutrition nor had an enteral tube placed. These cohorts were then compared regarding short- and long-term outcome, readmission rates, and surgical admission length of stay. We also investigated preoperative factors in order to attempt to identify patients that were more likely to receive parenteral nutrition.

Of those patients who underwent PD for pancreas cancer without enterostomy tube placement in California, only 18% received parenteral nutrition during the surgical admission. There was no significant difference in the short-term survival between groups, as indicated by no differences in the 30-day mortality. However, the patients who received parenteral nutrition showed a trend towards reduced long-term survival, although this difference was small and marginally significant. Obviously, this difference in the long-term survival could be attributed to either the postoperative complications that necessitated the use of parenteral nutrition or the higher CCI score in the parenteral nutrition group. Considering the equivalent survival data and the fact that less than 1 in 6 patients received parenteral nutrition, routine enterostomy tube placement in all patients would have over-treated more than 80% of the patients. In considering only the top quartile of hospitals performing PD for exocrine cancer of the pancreas, only 12% of patients received parenteral nutritional support, thus, strengthening the argument against the routine placement of enterostomy tubes.

Neither the parenteral nutrition nor the enterostomy tube groups showed an increase in readmissions when compared to the reference group that did not undergo nutritional support intervention. Therefore, it is unlikely that complications from parenteral or enteral nutrition, such as catheter sepsis or enterostomy tube complications, were a major contributor to reasons for readmission. Complications from the PD or the progression of disease were more likely to be reasons for readmission. Thus, the readmission rates do not yield evidence to support routine enteral tube placement.

Examination of the length of stay associated with the surgical admission demonstrated that the receipt of parenteral nutrition increased the median length of stay by 5 days compared to the reference group. However, it is important to note that the increased length of stay is most likely related to the complication that led to the parenteral nutrition, and not to the use of parenteral nutrition itself. The addition of a feeding tube increased the length of stay by 1 day when compared to the reference group. If one assumes that approximately 20% of the patients would require parenteral nutrition, as was the case when excluding the patients who underwent enterostomy placement, then this would amount to 1,435 (20% $\times$ 1435 $\times$ 5 days) additional days of admission compared to patients that did not receive parenteral nutrition. If we routinely placed jejunostomy tubes in all patients, then, by our data, this would result in increasing the length of stay by one day, and also would result in 1,435 (1435 $\times$ 1 day) additional hospital admission days. Thus, the length of stay arguments result in equivalency regarding the number of days of hospital admission.

Lastly, given equivalence regarding the short- and long-term survival and readmission rates, we attempted to define preoperative factors that would possibly guide the selective placement of feeding tubes. Multivariate logistical analysis was performed on preoperative factors in order to attempt to define a group of patients more likely to receive parenteral nutrition. A CCI of 3 or more was the strongest predictor of the receipt of parenteral nutrition, resulting in an approximately two-fold increase in the odds ratio (OR = 1.84, 95% CI: 1.20–2.85; $P < 0.005$). Thus, the selective placement of feeding tubes may be warranted in patients with significant comorbidities. Of note, diabetes and age were not independent predictors of receiving parenteral nutritional support.

This study is unique in that it utilized the California Office of Statewide Health Planning and Development (OSHPD) database linked to the California Cancer Registry database, allowing for the population-based analysis of pancreas cancer on a statewide level. There have been previous studies investigating pancreas cancer using administrative databases; however, these studies linked the Surveillance Epidemiology and End Results database (SEER) to Medicare data, which only captures the population over the age of 65 years [20]. Given that the median age in our study was 66 years, approximately half of the cohort would have been lost using SEER linked to Medicare data.

As with any study utilizing an administrative database, limitations of this study included bias associated with analyzing retrospective data. Our goal was to provide preliminary evidence of associations that could be verified through randomized controlled trials in order to determine causality. Additionally, although we were able to identify enterostomy tube placement by ICD-9 coding, we could not determine whether or not an enterostomy tube was utilized to deliver enteral tube feeding. Therefore, it is possible that some patients in the enterostomy group underwent enterostomy tube placement in anticipation of their needing nutritional support, but, in the end, did not receive enteral nutrition via the tube. Also, although we would have liked to have investigated the use of nasojejunal tube feeding, this was not possible due undercoding of this procedure in the dataset. Lastly, there was a small number of patients (56) who received parenteral nutrition and underwent enterostomy tube placement within the surgical admission. This use of both enteral and parenteral nutrition could be explained by patients receiving parenteral nutrition preoperatively and enteral nutrition postoperatively or tube malfunction necessitating parenteral nutritional support. From the data available, we were unable to discern the reasons for and the timing of nutritional support. Thus, these patients were excluded from the analysis. Similarly, we were unable to determine the timing of parenteral nutrition administration during the surgical admission. Some patients in the parenteral nutrition only cohort may have received parenteral nutrition prior to surgery, following surgery, or both. This limitation only serves to bias our post-PD parenteral utilization rate higher than the actual rate and, thus, only strengthens our conclusions. These limitations are in line with the goals of a study utilizing retrospective data to determine associations and on which to base a future randomized controlled trials, not a study to establish causality.

In summary, some surgeons routinely place jejunostomy tubes at the time of PD due to the benefits of enteral nutrition outweighing those of parenteral nutrition. The goal of this study was to evaluate whether or not this routine placement of enteral access was supported by the evidence from a population-based data set. Our results demonstrate that less than 1 in 6 patients require parenteral nutrition during the surgical admission. Therefore, the placement of routine enteral access would mean the overtreatment of approximately 80% of the patients undergoing PD for pancreas cancer. Neither the parenteral nutrition nor the enterostomy groups demonstrated any significant difference in perioperative mortality, long-term survival, or readmission rates when compared to patients that did not receive parenteral nutrition nor had an enterostomy tube placed. A preoperative CCI score ≥ 3 was determined to be a strong independent predictor of receiving parenteral nutrition. Given the known benefits of enteral nutrition over parenteral nutrition, a selective approach to the placement of an enterostomy tube may be warranted in patients at increased risk of needing nutritional support after PD for adenocarcinoma of the pancreas. This study is the first step in the resolution of the debate over routine enteral nutrition access placement following PD. Although randomized studies are necessary to prove causality, it seems that the routine placement of jejunostomy following PD is not supported by the evidence.

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