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Association for Academic Surgery

Mortality after pancreaticoduodenectomy: assessing early and late causes of patient death

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ARTICLE INFO

Article history:
Received 27 February 2018
Received in revised form
6 May 2018
Accepted 31 May 2018
Available online xxx

Keywords:
Pancreaticoduodenectomy
Whipple
Mortality
Complications
Outcomes
Quality improvement

ABSTRACT

Background: Safety of pancreaticoduodenectomy has improved significantly in the past 3 decades. Current inpatient and 30-d mortality rates are low. However, incidence and causes of 90-d and 1-y mortality are poorly defined and largely unexplored.

Methods: All patients who had pancreaticoduodenectomy between 2007 and 2016 were included in this single institution, retrospective cohort study. Distributions of pancreaticoduodenectomy-specific morbidity and cause-specific mortality were compared between early (within 90 d) and late (91-365 d) postoperative recovery periods.

Results: A total of 551 pancreaticoduodenectomies were performed during the study period. Of these, 6 (1.1%), 20 (3.6%), and 91 (16.5%) patients died within 30, 90, and 365 d after pancreaticoduodenectomy, respectively. Causes of early and late mortality varied significantly (all $P \leq 0.032$). The most common cause of death within 90 d was due to multisystem organ failure from sepsis or aspiration in 9 (45%) patients, followed by post-pancreatectomy hemorrhage in 5 (25%) patients, and cardiopulmonary arrest from myocardial infarction or pulmonary embolus in 3 (15%) patients. In contrast, recurrent cancer was the most common cause of death in 46 (65%) patients during the late postoperative period between 91 and 365 d. Mortality from failure to thrive and debility was similar between early and late postoperative periods (15% *versus* 19.7%, $P = 0.76$).

Conclusions: Most quality improvement initiatives in patients selected for pancreaticoduodenectomy have focused on reduction of technical complications and improvement of early postoperative mortality. Further reduction in postoperative mortality after pancreaticoduodenectomy can be achieved by improving patient selection, mitigating postoperative malnutrition, and optimizing preoperative cancer staging and management strategies.

Presented in part at the 13th Annual Academic Surgical Congress (ASC) January 30-February 1, 2018, in Jacksonville, Florida.

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https://doi.org/10.1016/j.jss.2018.05.075

Introduction

Mortality after pancreaticoduodenectomy has decreased considerably from as high as 25%-30% in the 1970-1980s to less than 2%-4% in the modern era.[1-4] The decline in short-term, perioperative mortality is observed across different indications for resection and variations of surgical technique.[3,5,6] Improvements in operative and anesthetic techniques, regionalization to high-volume centers, implementation of standardized recovery pathways, and better understanding and management of common complications have all contributed to the dramatic decline in postoperative mortality.[7-10]

While the decrease in postoperative mortality is encouraging, the definition of mortality used in many studies is limited to either in-hospital or within 30-d from the index operation.[3,4] Few studies explore surgery related mortality beyond immediate 30-day postoperative period; but in general, these studies report higher rates of patient death than 30-d or inpatient mortality.[11-13]

The primary objective of this study was to compare differences between early (defined as within 90 d of operation) and late (defined as between 91-365 d after operation) patient-specific mortality after pancreaticoduodenectomy. The secondary objective was to identify potentially modifiable factors that result in patient death.

Materials and methods

Patient population

This single institution, retrospective study included all adult patients (≥18 y of age) who underwent standard or pylorus-preserving pancreaticoduodenectomy for benign or malignant pathology between 2007 and 2016 at the University of Virginia Health System. The study was reviewed and approved by the University of Virginia Institutional Review Board for Health Sciences Research (protocol #19754). Abstracted demographic information included age, sex, and race/ethnicity. Pathologic diagnosis was defined based on postresection pathology and categorized as pancreatic adenocarcinoma (PDAC), other malignancies (e.g., duodenal cancer, periampullary cancer, neuroendocrine carcinoma, and others), premalignant neoplasms (e.g., intraductal papillary mucinous neoplasms without malignant transformation to carcinoma, premalignant duodenal adenomas, and others), and benign disease (e.g., chronic pancreatitis, serous cystadenoma, and others).

Outcome definitions

The primary outcome was patient-specific mortality categorized as early if it occurred between 0 and 90 d after pancreaticoduodenectomy and late if it occurred between 91 and 365 d after pancreaticoduodenectomy. Causes of mortality were categorized as (1) multisystem organ failure (MSOF) secondary to sepsis, aspiration, or hemorrhage; (2) cardiac arrest secondary to myocardial infarction or pulmonary embolus; (3) debility with failure to thrive; and (4) cancer recurrence. Secondary outcomes included causes of early and late morbidity, including technical complications such as pancreatic fistula, delayed gastric emptying (DGE), bile leak, gastrointestinal anastomotic leak, hemorrhage, and reoperations. Pancreatic fistula and DGE were categorized based on standardized International Study Group of Pancreatic Surgery definitions.[14,15] Bile leak was defined using the standardized guidelines from the International Study Group of Liver Surgery.[9] Reoperations related to pancreaticoduodenectomy were abstracted from clinical records. Indications for reoperation were categorized as hemorrhage, gastrointestinal complications (i.e., ischemia, anastomotic leak, perforation, obstruction), and abdominal wall incisional complications (i.e., dehiscence, evisceration, hernia).

Data analysis

Categorical variables were reported as percentages and compared using either chi-squared or Fisher's exact tests, as appropriate. Continuous data were summarized as median with interquartile range and compared with Wilcoxon rank-sum test. Statistical analyses were performed using Stata software, version 14.2 (StataCorp LP, College Station, TX), and P values less than 0.05 were considered significant.

Results

Patient demographics and clinical factors

A total of 551 patients, median age 65 y (interquartile range 57-73), underwent pancreaticoduodenectomy during the study period (Table 1). The majority of patients were men ($n = 300$, 54.4%) and white ($n = 483$, 87.7%). The most common indication for pancreaticoduodenectomy was pancreatic adenocarcinoma ($n = 226$, 41.0%), followed by other malignancy ($n = 182$, 33.0%). Proportions of postoperative complications are summarized in Table 1.

Early and late postoperative mortality

Of the 551 patients, 91 (16.5%) died within 1 y after pancreaticoduodenectomy (Table 1). Six patients (1.1%) died within 30 d of the index operation. Proportions of early and late mortality were 20 patients (3.6%) in the early (0-90 d postoperative period) and 71 patients (12.9%) in the late (91-365 d) postoperative period. Comparisons between the two groups are summarized in Table 2.

One-year mortality was lower in patients with benign or premalignant diagnosis compared to patients with PDAC or other malignancies (8.4% *versus* 19.4%, $P < 0.001$). One-year mortality was highest in patients with PDAC (23.5%). Of the 226 patients with PDAC, 174 (77%) received neoadjuvant therapy and 180 (79.6%) received adjuvant therapy. Adjuvant therapy was initiated in 2 of 9 (22.2%) PDAC patients who died in the early period and in 31 of 44 (70.5%) PDAC patients who died in the late period.

Causes of death are summarized in Table 3. MSOF and cardiac arrest were the most common causes of early mortality and were significantly more common in the early postoperative period (all $P \leq 0.032$). MSOF resulting from sepsis ($n = 6$, 30%), aspiration ($n = 3$, 15%), or hemorrhage ($n = 5$, 25%) were the