Published in final edited form as:

Am J Surg. 2016 August ; 212(2): 195–201.e1. doi:10.1016/j.amjsurg.2016.03.001.

Standardization of Surgical Care in a High-Volume Center Improves Survival in Resected Pancreatic Head Cancer

Daniel Delitto, M.D.^a, Brian S. Black, B.S.^a, Holly B. Cunningham, M.D.^a, Sarunas Sliesoraitis, M.D.^b, Xiaomin Lu, Ph.D.^c, Chen Liu, M.D., Ph.D.^d, George A. Sarosi, M.D.^{a,e}, Ryan M. Thomas, M.D.^{a,e}, Jose G. Trevino, M.D.^a, Steven J. Hughes, M.D.^a, Thomas J. George Jr, M.D.^b, and Kevin E. Behrns, M.D.^a

^aDepartment of Surgery, College of Medicine, University of Florida Health Science Center, Gainesville, FL 32610

^bDepartment of Medicine, College of Medicine, University of Florida Health Science Center, Gainesville, FL 32610

^cDepartment of Biostatistics & Children's Oncology Group, College of Public Health and Health Professions, University of Florida Health Science Center, Gainesville, FL 32610

^dDepartment of Pathology, College of Medicine, University of Florida Health Science Center, Gainesville, FL 32610

^eNorth Florida/South Georgia Veterans Health System, Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610

Abstract

Background—Durable clinical gains in surgical care are frequently reliant on well-developed standardization of practices. We hypothesized that the standardization of surgical management would result in improved long-term survival in pancreatic cancer.

Methods—Seventy-seven consecutive, eligible patients representing all patients who underwent PD and received comprehensive, long-term postoperative care at the University of Florida were analyzed. Patients were divided into pre- and post-standardization groups based on the implementation of a pancreatic surgery partnership, or standardization program.

Results—Standardization resulted in a reduction in median length of stay (10 vs. 12 d; $P=.032$), as well as significant gains in disease-free survival (DFS) (17 vs. 11 mo; $P=.017$) and overall survival (OS) (26 vs. 16 mo; $P=.004$). The improvement in OS remained significant on multivariate analysis (HR=0.46, $P=.005$).

Conclusions—Standardization of surgical management of PC was associated with significant gains in long-term survival. These results suggest strongly that management of pancreatic head

*Corresponding Author: Kevin E. Behrns, Department of Surgery, University of Florida College of Medicine, PO Box 100286, 1600 SW Archer Rd, Gainesville, FL 32610. kevin.behrns@surgery.ufl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

adenocarcinoma be standardized likely by regionalization of care at high performing oncologic surgery programs.

Keywords

centralization; standardization; pancreatic surgery; pancreatic cancer

Introduction

The complexity of intraoperative and postoperative care associated with pancreaticoduodenectomy (PD) has led to a growing emphasis on surgical specialization, which is supported by the numerous hepatobiliary and pancreatic surgery sub-specialty training programs that have arisen in the last two decades. Numerous single institution experiences have demonstrated superior short-term outcomes in specialized, high-volume pancreatic surgical centers.¹⁻¹⁰ The factors contributing to favorable outcomes in single centers, however, remain elusive but are important to discern because up to one quarter of patients will survive five years postoperatively with treatment at highly select centers.¹¹ The pathobiology of PC has challenged the development of effective systemic therapies. As a result PC is projected to be the second leading cause of cancer deaths by 2030 in the United States.¹² Therefore, efforts to understand modifiable clinical approaches that influence survival are warranted.

Emerging data indicate that centralization in pancreatic surgery consistently correlates with improved long-term survival in cancer.^{3, 2, 13} Regionalization of oncologic pancreatic head resections led to a marked survival improvement in a Dutch series of 2,129 pancreatic resections.¹³ In addition, results from the same group isolating cases of pancreatic head malignancies corroborated this correlation between high-volume hospitals and improved survival.¹⁴ Another large series analyzing 2,592 pancreatectomies for cancer through the National Medicare database has confirmed these findings.² However, though centralization of pancreatic surgery has led to improved results in high-volume institutions compared to low-volume institutions, the specific factors related to improved outcomes at these highly-specialized centers have not been detailed throughout the continuum of patient care.

The centralization of complex abdominal operations often includes standardization of postoperative management. Specifically, the implementation of clinical pathways in hepatobiliary and pancreatic surgery improved both short-term outcomes and costs associated with postoperative care at two major hepatobiliary surgical centers in the United States.^{15, 16} However, data remain limited as to whether a combination of centralization, defined here as the limitation of pancreatic surgery to high volume pancreatic surgeons, and standardization, or the implementation of operative and postoperative protocols based on consensus agreements between experienced pancreatic surgeons, leads to improved long-term outcomes.

To specifically address this question, we examined long-term outcomes in a consecutive series of pancreatic cancer patients, who underwent PD and subsequent long-term, comprehensive medical management at the University of Florida (UF). We purposefully selected patients that received the entirety of care at our institution to determine if the

outcomes differed from a previous institutional cohort and benchmarked with national high performing programs. Thus, these cohorts are a highly select group of patients to ensure consistent medical oncologic care, representing only 4% of patients undergoing PD at our institution over this time span. Patients were categorized into pre- and post-standardization groups based on the implementation of a pancreatic surgery partnership in 2008, reflecting standardization of operative and postoperative management. We hypothesized that standardization of care throughout the continuum of treatment would result in improved long-term survival in resected pancreatic cancer.

Methods

A retrospective review of an institutional review board-approved, prospectively maintained pancreatic cancer database at the University of Florida was conducted. All patients resected by PD with continued follow-up with the institution's medical oncologists were reviewed. Patients receiving neoadjuvant chemotherapy were excluded because most received therapy outside of our treatment center precluding standardization of care.

In 2008, the care of patients with complex surgical diseases, including pancreatic carcinoma, was grouped by clinical expertise resulting in multiple changes in and standardization of care (Supplemental Table S1). Measures undertaken in the partnership program included creation of a pancreas/biliary surgical service, concentration of PD to a few, highly experienced surgeons, standardized pathologic assessment, evidence-based pre- and postoperative care pathways, mandatory review at an institutional tumor board and postoperative oncologic follow-up with in-house medical oncologists. Environmental changes such as surgical, anesthesia, nursing and outpatient clinical staff was also restricted to consistent personnel with expertise in both the management of pancreatic surgical patients as well as postoperative oncologic care.

Postoperative complications were evaluated according to the previously validated Clavien-Dindo classification¹⁷, with a specific focus on pancreatic fistula, defined using the International Study Group on Pancreatic Fistula (ISGPF) criteria.¹⁸ Primary outcomes were postoperative disease-free survival (DFS) and overall survival (OS), where DFS is defined as the time from surgery to disease recurrence or death and OS is defined as the time from surgery to death.

All statistical analyses were performed using the SAS version 9.3. A p-value that was less than 0.05 was considered statistically significant. Continuous variables were compared between groups using the Wilcoxon rank sum test and categorical variables were analyzed using the exact Chi-square test. Survival curves were estimated using Kaplan-Meier methodology and compared using the log-rank test between groups. Univariate association of any continuous variable with DFS and OS, respectively, was performed using a Cox Proportional Hazards Regression Model. For assessing the effect of successful completion of three months of adjuvant chemotherapy on DFS/OS, patients who dropped out early or had DFS/OS events within 3 months (i.e. patients who were not at risk at 3 months) were excluded from the corresponding analysis. T stage was dichotomized to low (T1-2) and high (T3-4) due to the relative lack of T1 and T2 tumors and margin status was dichotomized to

R0 and non-R0 due to the low rate of R2 resections. All variables significant ($P < 0.05$) on univariate analysis were included in multivariate Cox Regression Model.

Results

In total, 77 patients received comprehensive oncologic care at the University of Florida for pancreatic head cancer from 2000 through 2012. Of these patients, 40 underwent PD prior to the implementation of the pancreatic surgery partnership (Pre-Standardization) and 37 underwent PD post-standardization (Post-Standardization). Preoperative clinical parameters for each group are displayed in Table 1. Groups were similar in presentation by age, comorbidities, body mass index (BMI), tobacco use and preoperative CA 19-9 concentrations. Of note, the post-standardization group contained a higher proportion of female patients (62.2% vs. 37.5%; $P = 0.041$). T stage was similar between groups, with the vast majority of patients presenting with T3-4 lesions (91.9% vs. 90.0%; $P = 1.000$). Groups were comparably distributed between N0 and N1 stages (70.3% N1 vs. 72.5% N1; $P = 1.000$).

Importantly, lymph node yield nearly doubled post-standardization (17.6 ± 0.9 vs. 9.1 ± 1.1 ; $P < .001$) (Table 2). The number of lymph nodes containing malignancy was similar between groups (2.5 ± 0.4 vs. 1.7 ± 0.3 ; $P = .201$). However, the ratio of positive lymph nodes to total lymph nodes slightly decreased ($0.14 \pm .02$ vs. $0.19 \pm .03$; $P = .159$). It is particularly interesting to note the change in predictive power of the positive lymph node ratio (LNR) post-standardization. Indeed, application of a Cox proportional hazards model to both pre- and post-standardization groups revealed a significant increase in the predictive power of the positive LNR in both DFS (HR 47.9; $P = .001$ vs. HR 0.9; $P = .942$) and OS (HR 33.1; $P = .012$; HR 0.6; $P = .0606$). This confirms previous findings that a focus on adequate lymph node harvest and pathologic examination markedly improves the accuracy of PC staging.^{19, 20}

Standardization resulted in a trend toward improved margin-free resection rate (73.0% vs 57.5%, $P = .232$) (Table 2), but this failed to reach statistical significance. As the indication for vascular resection likely represents a more aggressive underlying disease burden²¹, we included this in our analysis, which revealed similar rates of major vascular resection in each group (16.2% vs. 12.5%; $P = .750$). Finally, adjuvant chemoradiation therapy was employed at similar rates after vs before standardization (chemotherapy administered to 86.5 vs 80%; $P = .549$ and radiation to 54.1 vs. 72.5%; $P = .104$). A higher proportion of patients in the post-standardization group achieved at least three months of postoperative chemotherapy, but this difference was not statistically significant in our analysis (70.3% vs. 52.5%; $P = .160$).

Operative complications were analyzed using the Clavien-Dindo classification¹⁷ with a specific focus on pancreatic fistulas, graded according to the International Study Group on Pancreatic Fistula (ISGPF) criteria (Table 2).¹⁸ The incidence of both grade A as well as grade B-C fistulas did not differ significantly. Similarly, no significant difference was observed between groups in the rate of major morbidity, defined as Clavien III/IV complications (24.3% vs. 17.5%; $P = .577$). Notably, standardized clinical pathways resulted

in significantly reduced postoperative hospital stays (median LOS 10 vs. 12 days; $P=0.032$).

A significant improvement in survival was noted in the post-standardization group (Fig. 1, Table 3). Median DFS in the post-standardization group was approximately 17 months vs. 11 months for the pre-standardization group ($P=0.017$). Similar improvement in OS was observed, in which the median time to death was approximately 26 vs. 16 months ($P=0.004$). Median follow-up was slightly greater for the post-standardization group (24 vs. 16 months; $P=.204$), which likely reflects the prolonged survival observed in this cohort. Importantly, this reduces the possibility of a bias favoring the post-standardization cohort in that these patients are more likely to be alive at the time of analysis due to the more recent presentation of their disease.

On univariate analysis, positive lymph node ratio was a predictor of DFS (HR 4.99; $P=0.034$) and successful completion of three months of adjuvant chemotherapy was a predictor of prolonged OS (HR 0.53; $P=0.019$). No other factors significantly associated with DFS or OS at an alpha level of 0.05 (Table 4). Variables that were significant ($P < 0.05$) in univariate analysis of DFS/OS were included in respective multivariate analyses. Multivariate analysis using a Cox proportional hazards model again demonstrated an association between receiving at least three months of adjuvant chemotherapy and OS (HR 0.54; $P=.024$). Importantly, multivariate analysis demonstrated a statistically significant association between surgical standardization and overall survival (HR 0.44; $P=.003$). This work therefore demonstrates a significant, clinically meaningful improvement in long-term survival following surgical standardization of pancreatic cancer management.

Discussion

Our data demonstrate that standardization in the operative management of PC at the single institution level led to significant gains in long-term survival, which was independent of known prognostic clinicopathologic factors. Throughout the time periods specified in the analysis (both pre and post-standardization), the institutional practice remained consistent with published NCCN guidelines regarding the role, type and modality of adjuvant therapy recommended for patients upon surgical recovery. In general, single agent fluoropyrimidine (5-FU) or gemcitabine was used uniformly as chemotherapy for 4-6 months. Standard fractionation of adjuvant radiotherapy was reserved for patients with close ($<1\text{mm}$) or positive margins or patients with node positive disease. Thus, these findings support an approach to centralize the treatment of pancreatic head cancer to oncologic centers that practice multidisciplinary care through standardized clinical protocols.

Standardization resulted in a doubling of the median number of lymph nodes resected and examined, thus markedly improving the prognostic capability of nodal staging in both disease-free and overall survival. These findings suggest that appropriate lymphadenectomy and pathologic examination are essential in order to properly stage PC. Multiple investigations have demonstrated that lymphadenectomy yields of at least 10 lymph nodes correlate with improved staging accuracy as well as improved long-term survival in PC.^{19, 22} However, multiple trials analyzing extended lymphadenectomies failed to show long-term

gains in PC.²³⁻²⁵ Remarkably, standardization in our group led to the examination of at least ten lymph nodes in 95% of patients.

Notably, our data demonstrated that resection margin displayed no significant correlation with either DFS or OS.²⁶ However, this may reflect evolving approaches to pathologic examination. Specific examination of the retroperitoneal margin occurred in approximately half of patients in the pre-standardization group. This may have led to a falsely elevated R0 resection rate, similar to the phenomenon observed regarding adequate lymph node harvest and examination.

Multivariate analysis demonstrated a significant correlation between the completion of at least three months of adjuvant chemotherapy and prolonged OS. Importantly, patients who initiated but failed to receive three months of adjuvant chemotherapy uniformly experienced a decline in clinical status, which ultimately led to the discontinuation of cytotoxic therapy. Medical oncologic practices with respect to adjuvant regimens did not change over this time. Therefore, this variable likely represents a better performance status postoperatively, which may reflect improved convalescence from major surgery.

Limitations of this investigation include a relatively small sample size in the setting of a single institution's experience, thus potentially limiting conclusions endorsing broad application of these standardization principles. However, our limited sample size underscores an extensive exclusion process in order to best control our analysis. While our institution performs approximately 180 pancreatic resections per year, our final study population included only 77 patients. This highly select group was chosen based on consistent medical oncologic care, as these patients continued to follow-up at our institution throughout the study time period. Thus, selecting only 4% of total PDs performed at our institution over 12 years represents a rigorous exclusion process performed in a prospective manner to focus on operative and long-term oncologic outcomes.

Conclusion

In summary, we demonstrate standardization in the surgical management of PC is independently associated with prolonged overall survival. Our findings corroborate those of larger series in a controlled, single institution environment. These data speak to potential gains from standardized approaches to pancreatic surgery on a more global scale, as additional methods to improve survival in PC represent a pressing clinical need.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the National Cancer Institute (NCI 5T32CA106493-09), Cracchiolo Foundation and Frederick A. Collier Surgical Society for their support in these investigations.

References

1. Teh SH, Diggs BS, Deveney CW, et al. Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines. *Arch Surg.* 2009; 144:713–21. [PubMed: 19687374]
2. Fong Y, Gonen M, Rubin D, et al. Long-term survival is superior after resection for cancer in high-volume centers. *Ann Surg.* 2005; 242:540–4. discussion 4-7. [PubMed: 16192814]
3. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. *N Engl J Med.* 2003; 349:2117–27. [PubMed: 14645640]
4. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg.* 1998; 228:429–38. [PubMed: 9742926]
5. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg.* 1997; 226:248–57. discussion 57-60. [PubMed: 9339931]
6. McPhee JT, Hill JS, Whalen GF, et al. Perioperative mortality for pancreatectomy: a national perspective. *Ann Surg.* 2007; 246:246–53. [PubMed: 17667503]
7. Gordon TA, Bowman HM, Tielsch JM, et al. Statewide regionalization of pancreaticoduodenectomy and its effect on in-hospital mortality. *Ann Surg.* 1998; 228:71–8. [PubMed: 9671069]
8. Kotwall CA, Maxwell JG, Brinker CC, et al. National estimates of mortality rates for radical pancreaticoduodenectomy in 25,000 patients. *Ann Surg Oncol.* 2002; 9:847–54. [PubMed: 12417505]
9. Rosemurgy AS, Bloomston M, Serafini FM, et al. Frequency with which surgeons undertake pancreaticoduodenectomy determines length of stay, hospital charges, and in-hospital mortality. *J Gastrointest Surg.* 2001; 5:21–6. [PubMed: 11309644]
10. Lieberman MD, Kilburn H, Lindsey M, et al. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg.* 1995; 222:638–45. [PubMed: 7487211]
11. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin.* 2014; 64:9–29. [PubMed: 24399786]
12. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014; 74:2913–21. [PubMed: 24840647]
13. Lemmens VE, Bosscha K, van der Schelling G, et al. Improving outcome for patients with pancreatic cancer through centralization. *Br J Surg.* 2011; 98:1455–62. [PubMed: 21717423]
14. Gooiker GA, Lemmens VE, Besselink MG, et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg.* 2014
15. Pitt HA, Murray KP, Bowman HM, et al. Clinical pathway implementation improves outcomes for complex biliary surgery. *Surgery.* 1999; 126:751–6. discussion 6-8. [PubMed: 10520925]
16. Porter GA, Pisters PW, Mansyur C, et al. Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. *Ann Surg Oncol.* 2000; 7:484–9. [PubMed: 10947015]
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; 240:205–13. [PubMed: 15273542]
18. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery.* 2005; 138:8–13. [PubMed: 16003309]
19. Ashfaq A, Pockaj BA, Gray RJ, et al. Nodal Counts and Lymph Node Ratio Impact Survival After Distal Pancreatectomy for Pancreatic Adenocarcinoma. *J Gastrointest Surg.* 2014
20. Huebner M, Kendrick M, Reid-Lombardo KM, et al. Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. *J Gastrointest Surg.* 2012; 16:920–6. [PubMed: 22421988]
21. Castleberry AW, White RR, De La Fuente SG, et al. The impact of vascular resection on early postoperative outcomes after pancreaticoduodenectomy: an analysis of the American College of

- Surgeons National Surgical Quality Improvement Program database. *Ann Surg Oncol*. 2012; 19:4068–77. [PubMed: 22932857]
22. Hellan M, Sun CL, Artinyan A, et al. The impact of lymph node number on survival in patients with lymph node-negative pancreatic cancer. *Pancreas*. 2008; 37:19–24. [PubMed: 18580439]
23. Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery*. 2005; 138:618–28. discussion 28-30. [PubMed: 16269290]
24. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. *Ann Surg*. 1998; 228:508–17. [PubMed: 9790340]
25. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periaampullary adenocarcinoma--part 3: update on 5-year survival. *J Gastrointest Surg*. 2005; 9:1191–204. discussion 204-6. [PubMed: 16332474]
26. Cameron JL, Riall TS, Coleman J, et al. One thousand consecutive pancreaticoduodenectomies. *Ann Surg*. 2006; 244:10–5. [PubMed: 16794383]

Figure 1. Kaplan-Meier Survival Curves

77 patients who underwent PD for PC were followed postoperatively from 2000 to 2012. The time of standardization corresponds to the implementation of a pancreatic surgery partnership. Kaplan-Meier survival curves were generated for DFS and OS and compared using the log-rank test. Significance was considered for $P < 0.05$.

Table 1
Patient Demographics and Staging

Parameter	Pre-Standardization (n = 40)	Post-Standardization (n = 37)	P Value
Age, mean (SE), y	64.0 (1.4)	65.1 (1.7)	.650
BMI, mean (SE)	25.9 (0.9)	24.8 (0.8)	.592
Male, %	25 (62.5)	14 (37.8)	.041
History of Smoking, %	23 (57.5)	26 (7.3)	.343
Charlson Comorbidity Index, mean (SE)	5.3 (0.2)	5.7 (0.21)	.216
*Preoperative CA 19-9, mean (SE), U/mL	2356.7 (1529.7)	1837.5 (1222.8)	.925
*CA 19-9 > 48 U/mL, %	21 (75.0)	29 (80.6)	.762
T Stage			
T1-2	4 (10.0)	3 (8.1)	1.000
T3-4	36 (90.0)	34 (91.9)	
N Stage			
N0	11 (27.5)	11 (29.7)	1.000
N1	29 (72.5)	26 (70.3)	

* Preoperative CA 19-9 values were not available for thirteen patients. 48 U/mL was a cutoff set by ROC analysis of CA 19-9 and DFS as described.

Abbreviation: BMI, body mass index; SE, standard error of the mean; IQR, interquartile range.

Table 2
Operative Factors and Postoperative Outcomes

Parameter	Pre-Standardization (n = 40)	Post-Standardization (n = 37)	P Value
Major vascular resection, %	5 (12.5)	6 (16.2)	.750
Total lymph nodes examined, mean (SE)	9.1 (1.1)	17.6 (0.9)	<.001
Positive lymph nodes, mean (SE)	1.7 (0.3)	2.5 (0.4)	.201
Positive lymph node ratio, mean (SE) *	0.19 (0.03)	0.14 (0.02)	.159
Retroperitoneal margin examined, %	20 (50.0)	37 (100.0)	<.001
R0 resections, %	23 (57.5)	27 (73.0)	
R1 resections, %	15 (37.5)	10 (27.0)	.205
R2 resections, % [#]	2 (5.0)	0 (0.0)	
Initiated adjuvant chemotherapy, %	32 (80.0)	32 (86.5)	.549
>3 mo adjuvant chemotherapy, %	21 (52.5)	26 (70.3)	.160
Adjuvant radiation, %	29 (72.5)	20 (54.1)	.104
Complications			
Length of stay, median (SE), d	12 (0.9)	10 (1.7)	.033
Pancreatic fistula, %	7 (17.5)	9 (24.3)	.461
Grade B/C fistula, %	4 (10.0)	6 (16.2)	.507
90-day morbidity			
Minor (Clavien I/II), %	22 (55.0)	18 (48.6)	.311
Major (Clavien III/IV), %	7 (17.5)	9 (24.3)	.461
90-day mortality, %	0 (0.0)	1 (2.7)	.481

* Positive lymph node ratio is defined as the number of lymph nodes positive for malignancy divided by the total number of lymph nodes examined by the pathologist.

[#] R2 resection is defined as a grossly positive margin.

Abbreviation: SE, standard error of the mean; d, day.

Table 3
Disease-free and Overall Survival

Outcome	Pre-Standardization (n = 40)	Post-Standardization (n = 37)	P Value
Follow-up duration, median months	16.1	24.0	.204
Disease-free survival, median months	10.9	16.7	
1-year DFS, % (SE)	45.0 (7.9)	62.2 (8.0)	.017
3-year DFS, % (SE)	12.5 (5.2)	27.2 (7.7)	
5-year DFS, % (SE)	5.0 (3.5)	27.2 (13.4)	
Overall survival, median months	16.1 (3.6)	26.0 (12.1)	
1-year OS, % (SE)	75.0 (6.8)	81.8 (5.5)	.004
3-year OS, % (SE)	15.0 (5.6)	48.9 (9.7)	
5-year OS, % (SE)	5.0 (3.4)	40.8 (15.7)	

Median follow-up duration, DFS and OS are displayed for each cohort as well as actuarial 1-, 3-, and 5-year survival. Abbreviations: SE, standard error of the mean.

Table 4

Univariate and Multivariate Analyses

Univariate Analysis	Disease-free Survival				Overall Survival			
	Hazard Ratio	95% CI	P Value		Hazard Ratio	95% CI	P Value	
PD post-standardization	0.55	.33	.90	.017	0.46	.27	.79	.004
Gender (Male)	0.99	.61	1.63	.980	1.14	.69	1.91	.609
Charlson Comorbidity Index	0.88	.73	1.06	.179	0.91	.74	1.12	.364
High T stage (T3-4)	1.47	.59	3.68	.403	1.75	.63	4.83	.276
N stage (N1)	1.51	.87	2.64	.145	1.43	.80	2.55	.226
Positive lymph node ratio	4.99	1.13	22.0	.034	4.11	.90	18.7	.067
Preoperative CA 19-9 > 48 U/mL	1.97	.95	4.07	.067	2.11	.98	4.56	.058
Positive margin	0.93	.55	1.56	.783	1.18	.69	2.02	.542
Initiated adjuvant chemotherapy	1.21	.60	2.46	.593	0.93	.45	1.90	.837
>3 mo adjuvant chemotherapy	0.62	.37	1.05	.071	0.53	.31	.91	.019
Adjuvant radiation therapy	1.15	.68	1.94	.601	1.27	.74	2.20	.389
Multivariate Analysis: DFS								
PD post-standardization	0.52	.30	0.90	.020				
Positive Lymph Node Ratio	2.0	.40	9.7	.411				
Multivariate Analysis: OS								
PD post-standardization					0.44	.25	.76	.003
>3 mo adjuvant chemotherapy					0.54	.31	.92	.024

77 patients undergoing PD for PC were followed postoperatively between 2000 and 2012. Survival analysis was performed using a univariate Cox proportional hazards model. Variables demonstrating significant associations with DFS/OS on univariate analysis ($P < 0.05$) were incorporated into respective multivariate analyses using a Cox proportional hazards model. CA 19-9 cutoff of 48 U/mL was established by ROC analysis of overall survival. Significance was considered for $P < 0.05$. Abbreviations: CI, confidence interval; HR, hazard ratio.