Factors Associated with Improved Survival after Resection of Pancreatic Adenocarcinoma

A Multivariable Model

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ABSTRACT

Background: Several retrospective studies suggest that perioperative care and anesthetic management for cancer resection may influence cancer recurrence or patient survival. Various intraoperative techniques such as paravertebral blocks, decreased opioid use, immunomodulation, and perioperative antiinflammatory administration, have previously been assessed for improved patient survival. The aim of this study was to assess associations between perioperative management and survival in patients undergoing resection of pancreatic adenocarcinoma.

Methods: Survival data and anesthetic records for 144 patients who had surgical resection of pancreatic adenocarcinoma from 2001 to 2012 were obtained and associations were sought between survival and 19 predefined variables. The authors performed a propensity weighted multivariable statistical analysis using Cox proportional hazards.

Results: Median length of survival was 562 days with 95% confidence interval (471, 680). In a multivariable Cox proportional hazard model of survival, the authors found increased survival in patients who received perioperative epidural analgesia and/or intraoperative dexamethasone. There was a 44% hazard ratio reduction, hazard ratio = 0.56, 95% confidence interval (0.38, 0.87), with dexamethasone. Adjuvant postoperative chemotherapy was associated with longer survival. A decrease in survival was noted in patients who received intraoperative blood transfusions, had poorer histologic grade, and advanced tumor stage.

Conclusions: The authors report an association between perioperative dexamethasone administration and improved survival in human pancreatic adenocarcinoma patients. An association between use of epidural anesthesia during primary pancreatic cancer surgery and prolonged survival was also observed. Previously identified associations between perioperative blood transfusions and poor tumor histologic grade and decreased survival were confirmed. Further investigations regarding the use of perioperative dexamethasone and neuraxial anesthesia in this patient population are warranted. **(Anesthesiology 2015; 122:317-24)**

As the fourth leading cause of cancer death in the United States, pancreatic adenocarcinoma is a devastating disease with an average 5-yr survival of 6%.[1] In 2014, an estimated 39,590 patients will die of this disease in the United States, accounting for approximately 7% of all cancer deaths.[1] Surgical intervention is a central part of the treatment for many cancers, including pancreatic adenocarcinoma. After complete resection of pancreatic cancer, the outcome remains relatively poor with a median survival from date of diagnosis of only 20 to 22 months.[2–4]

Both retrospective human studies and prospective animal studies suggest that perioperative care and anesthetic management for cancer resection may have effects on cancer recurrence or patient survival. Paravertebral blocks,[5,6] perioperative ketorolac,[7] epidural analgesia,[8] and timing of epidural use[9] have each been associated with improved outcomes for different cancer surgeries. Several possible mechanisms have been proposed to explain these observed associations including decreased opioid intake,[10] local anesthetic effects,[5] antiinflammatory effects,[11] immunomodulation,[12] and a decrease in the stress response.[13] Consistent

What We Already Know about This Topic

- Retrospective studies have found perioperative care and anesthetic management affected cancer recurrence and survival in patients undergoing cancer resection surgery
- It is unknown if the immunosuppressive effects of dexamethasone would decrease survival or if its antiinflammatory effects would improve survival

What This Article Tells Us That Is New

- A model based on retrospective analysis of the records of 144 patients who underwent resection of pancreatic adenocarcinoma between 2001 and 2011 predicted median survival of patients to whom dexamethasone is administered and who have epidural analgesia would be increased from 370 days to 651 days compared to similar patients receiving neither dexamethasone nor epidural analgesia

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with the last three mechanisms, animal studies suggest a potential benefit of dexamethasone in reducing pancreatic adenocarcinoma dissemination.[14]

Improved understanding of the effects of perioperative management on patients' cancer recurrence and survival could lead to improved outcomes and survival. The aim of this study was to assess for associations between perioperative management and survival in patients undergoing resection of pancreatic adenocarcinoma.

Materials and Methods

Approval to conduct this study was obtained by the University of Utah Institutional Review Board (Salt Lake City, Utah; Institutional Review Board number 00056363).

We obtained data from the Cancer Clinical Research Information System for 170 patients having had surgical resection of pancreatic adenocarcinoma from 2001 to 2012 and linked that data to the respective anesthetic record. Twenty-six patient records were excluded for being insufficiently complete or illegible. Of the remaining 144 patients, all had undergone primary resection in the University of Utah Health Care System (either the University Hospital or the Huntsman Cancer Hospital), and had sufficiently complete anesthetic records for analysis.

The following covariates were chosen to be included in the analysis because of their possible influences on inflammation, immune response, and/or survival. These include: (1) CA19-9 just before resection; (2) age; (3) sex; (4) American Society of Anesthesiology Physical Status; (5) presence of diabetes mellitus; (6) preoperative administration of neoadjuvant chemotherapy; (7) body mass index; (8) preoperative plasma albumin concentration; (9) preoperative hematocrit; (10) intraoperative dexamethasone administration; (11) use of epidural analgesia; (12) histologic grade of tumor; (13) presence of margin involvement in resected specimen; (14) tumor stage; (15) maximum size of tumor; (16) perioperative transfusion of erythrocytes; (17) intraoperative administration of fentanyl or sufentanil; (18) intraoperative administration of morphine or hydromorphone; and (19) use of postoperative adjuvant chemotherapy.

Statistical Analysis

Descriptive statistics included mean, median, interquartile range, 95% confidence interval (CI), and event rates. Two patients had one missing value in the perioperative covariates that was imputed to the median value. No values were imputed for missing data in preoperative covariates. Survival data were right censored at the date of the last clinic visit. Univariable comparison of survival for dexamethasone administration was by a Kaplan–Meier estimator with a log-rank test statistic and by Cox proportional hazards (CPH) regression with estimation of the hazard ratio (HR). Nine preoperative covariates (see Materials and Methods) were identified as possibly having a different distribution of values between those receiving and not receiving dexamethasone and that also might have an influence on survival (table 1). To remove confounding by these factors, an average treatment effect propensity score was estimated for the probability of receiving/not receiving dexamethasone regressed on these nine factors by nonparsimonious boosted logistic regression analysis; interaction between factors was allowed; the mean of the absolute standardized mean difference was used as the stopping rule. Diagnostic checks of the propensity scores included the balance statistics, the probability value of the standardized effect sizes, and the distribution of propensity scores.[15]

Multivariable CPH models were estimated using inverse probability weighting with the average treatment effect propensity scores. Compared to various types of matching by propensity scores to create subsets of treatment and control groups, inverse probability weighting negates the necessity of removing cases that cannot be matched; all cases were included in the CPH models. The initial CPH model was forced to include 10 operative and postoperative factors (see Materials and Methods), which may influence inflammation, immune response, and/or survival. These were: (1) dexamethasone; (2) the use of epidural analgesia; (3) the histologic grade of the tumor; (4) the presence of margin

Table 1. Distribution of Covariates for Propensity Score Estimation

Covariate	Dexamethasone Yes (n = 69)	Dexamethasone No (n = 75)
CA19-9 (at resection), median (IQR)	133 (25, 307)	108 (35, 479)
Age (yr), median (IQR)	65 (56, 72)	67 (61, 73)
Sex (male/female)	33/36	43/32
ASA status	II 21	II 18
	III 47	III 50
	NA 1	NA 7
Presence of diabetes mellitus, n (%)	15 (22%)	26 (35%)
Neoadjuvant chemotherapy, n (%)	23 (33%)	17 (23%)
Body mass index, median (IQR)	26 (22.7, 28.5)	25.3 (23.3, 28.0)
Preoperative plasma albumin concentration, median (IQR)	3.8 (3.5, 4.0)	3.7 (3.5, 4.0)
Preoperative hematocrit, median (IQR)	38 (35, 41)	39 (35, 41)

ASA = American Society of Anesthesiologists; IQR = interquartile range; NA = data missing.

Table 2. Covariates in Multivariable Cox Proportional Hazards Model

Covariate	Dexamethasone Yes (n = 69)	Dexamethasone No (n = 75)
Perioperative epidural analgesia, n (%)	53 (77%)	58 (77%)
Histologic grade of tumor, n (%)	g1 5 (7%)	g1 6 (8%)
	g2 33 (48%)	g2 40 (53%)
	g3 31 (45%)	g3 29 (39%)
Margin involvement of resected specimen, n (%)	12 (17%)	24 (32%)
Tumor stage	ia 2	ia 5
	ib 4	ib 4
	iia 16	iia 10
	iib 38	iib 44
	iii 6	iii 12
	iv 3	iv 0
Maximum size of tumor (cm), median (IQR)	2.2 (2, 4)	3 (2, 4)
Perioperative transfusion of erythrocytes (# units), median (IQR)	0 (0, 0)	0 (0, 0.5)
	17 patients received 1 to 17 units	19 patients received 1 to 13 units
Intraoperative administration of fentanyl or sufentanyl (fentanyl equivalents, mcg), median (IQR)	1000 (550, 1,575)	800 (575, 1,188)
Intraoperative administration of morphine or hydromorphone (morphine equivalents, mg)	0 (0, 0)	0 (0, 0)
	8 patients received doses up to 13	15 patients received doses up to 13
Postoperative adjuvant chemotherapy, n (%)	36 (52%)	21 (28%)

IQR = interquartile range.

involvement in the resected specimen; (5) the tumor stage; (6) the maximum size of the tumor; (7) the transfusion of erythrocytes; (8) intraoperative administration of fentanyl or sufentanil; (9) intraoperative administration of morphine or hydromorphone; and (10) the use of postoperative adjuvant chemotherapy (table 2). The assumed potency ratios were sufentanil/fentanyl = 7.5 and hydromorphone/morphine = 6.67. The overall fit of CPH models was reported by a Wald statistic; the individual HR coefficients were interpreted by a Wald Z score statistic. Robust estimation of the covariance matrix was used giving larger standard errors. Statistical significance was set at an alpha of 0.05.

In hypothesis testing, type I (rejection of the null hypothesis when it is in fact true) and type II (failure to reject the null hypothesis when it is in fact false) errors must be controlled; 1 minus the type II error rate is power. There is a multiple testing problem inherent in the coefficients of a multivariable regression model, as each coefficient is a null hypothesis in a separate statistical test. Some regression coefficients may be statistically significant purely by chance. A familywise error rate procedure such as the Bonferroni correction seeks to reduce the probability of even one false discovery (type I error); this is considered a conservative procedure that increases the type II error with loss of power. By contrast, false discovery rate (FDR) procedures are designed to control the expected proportion of incorrectly rejected null hypotheses; FDR procedures have greater power. The Benjamini–Yekutieli step-up procedure was applied to the *P* values of regression coefficients in the CPH models. This Benjamini–Yekutieli step-up procedure ensures that the FDR is correctly adjusted for any dependency structure of a set of regression coefficients. The alpha level at which the FDR was controlled was set at 0.05; that is to say, the expected proportion of incorrectly rejected null-hypotheses is 5%.[16]

Concerning the possible survival benefits of dexamethasone, sample sizes and statistical power were calculated for proportional hazard modeling of observational survival analyses and randomized controlled trials using methods by Latouche *et al.*[17] Two sided tests were used with the type I error rate alpha set at 0.05.

Kaplan–Meier and CPH estimators were done in the survival package.* The twang package was used for propensity score estimation.† Propensity weighted CPH modeling, prediction of median survival, and survival plots were done in the survey package.‡ The multiple testing procedure was done in the mutoss package.§ Power and sample size calculations for survival models were done in the powerSurvEpi package.‖ All functions were run in the public domain R statistical platform.#

* Therneau T (2014). survival: A package for survival analysis in S. R package version 2.37-7. Available at: http://CRAN.R-project.org/package=survival. Accessed December 17, 2014.

† Ridgeway G, McCaffrey D, Morral A, Ann B, Burgette L (2014). twang: Toolkit for weighting and analysis of nonequivalent groups. R package version 1.4-0. Available at: http://CRAN.R-project.org/package=twang. Accessed December 17, 2014.

‡ Lumley T (2014). survey: Analysis of complex survey samples. R package version 3.30. Available at: http://CRAN.R-project.org/package=survey. Accessed December 17, 2014.

§ Blanchard G, Dickhaus T, Hack N, Konietschke F, Rohmeyer K, Rosenblatt J, Scheer M, Werft W (2014). mutoss: Unified multiple testing procedures. R package version 0.1-8. Available at: http://CRAN.R-project.org/package=mutoss. Accessed December 17, 2014.

‖ Qiu W, Chavarro J, Lazarus R, Rosner B, Ma J (2012). powerSurvEpi: Power and sample size calculation for survival analysis of epidemiological studies. R package version 0.0.6. Available at: http://CRAN.R-project.org/package=powerSurvEpi. Accessed December 17, 2014.

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. R version 3.1.1. Available at: http://www.R-project.org. Accessed December 17, 2014.

Results

Of the 144 cancer patients in our study, 69 received between 1 and 10 mg dexamethasone intraoperatively; 75 received none. More specifically, 32 patients received 4 mg, 1 patient received 5 mg, 19 patients received 6 mg, 16 patients received 8 mg, and 1 patient received 10 mg of dexamethasone.

Median follow-up was 437 days with interquartile range (243, 831). The longest follow up was censored at 2,885 days. There were 102 reported death dates in the 144 patients (71% mortality); mortality for those receiving and not receiving dexamethasone was 41/69 (59%) and 61/75 (81%), respectively. Overall, the median survival time from resection date to death date was 562 days with 95% CI (471, 680). Dexamethasone administration improved median survival by Kaplan–Meier univariable analysis (622, 95% CI [520, 1,091] days *vs.* 479, 95% CI [383, 655] days; $P = 0.01$) (fig. 1). A univariable CPH model demonstrated a HR of 0.60 with 95% CI (0.40, 0.90) favoring the administration of dexamethasone.

The distribution of perioperative covariate values was similar between those receiving and not receiving dexamethasone with the exception of the percentage with margin involvement and postoperative chemotherapy (table 2). In the propensity score, four (preoperative plasma albumin concentration, preresection CA19-9, American Society of Anesthesiologists Status, body mass index) of the nine covariates accounted for about 85% of influence in estimating the probability of treatment assignment. There were sufficient iterations in the regression algorithm to adequately explore the balance space (mean of the absolute standardized mean differences). None of the standardized effect sizes (unweighted or weighted by propensity score) comparing the nine covariates between patients receiving or not receiving dexamethasone were statistically significant. The propensity weighted mean standardized effect size was reduced from 28 to 21% over the nine covariates. The effective sample size of the treatment groups was maintained at approximately the nominal size.

In a propensity inverse weighted CPH model (Model 1, table 3), six covariates were associated with survival differences; the overall model achieved statistical significance (Wald test = 96.2, $P = 10^{-13}$). There was improved survival in patients who had received intraoperative dexamethasone with a 42% HR reduction (HR = 0.58, 95% CI [0.38, 0.89]; $P = 0.013$). Patients who did not receive a perioperative epidural had decreased survival with a 95% HR increase (HR = 1.94, 95% CI [1.07, 3.52]; $P = 0.029$). Postoperative chemotherapy, lower tumor stage, lower tumor grade, and fewer units transfused intraoperatively were all associated with increased survival. The involvement of tumor in the resected margin, the maximum tumor size, and the mass of administered fentanyl equivalents and morphine equivalents all had HRs close to the line of identity and far from statistical significance.

To refine the model, a second CPH model was estimated without the four nonsignificant covariates; coefficient values for the remaining six covariates had small changes from those in Model 1 and remained statistically significant. To check for a multiple testing problem, the Benjamini–Yekutieli step-up procedure for controlling the FDR was applied to the

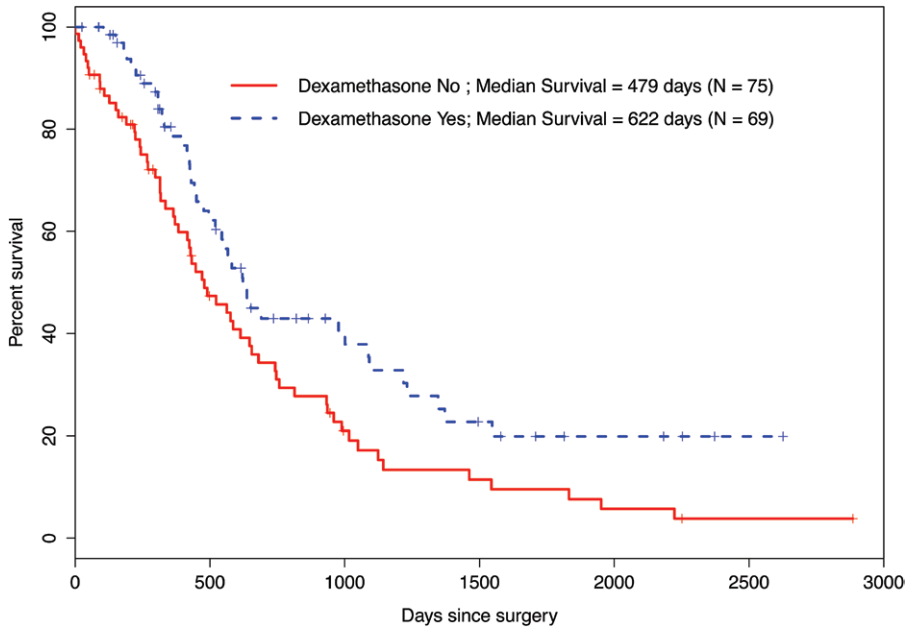

Fig. 1. Survival in patients who received *versus* did not receive intraoperative dexamethasone. Patients who received dexamethasone showed improved survival, defined as days from date of resection to death date ($P = 0.0112$).

Table 3. Perioperative Risk Factors and Their Association with Patient Survival

	Model 1 (10 Covariates) Overall Model Fit Wald Test = 96.2, df = 15, $P = 10^{-13}$		Model 2 (6 Covariates) Overall Model Fit Wald Test = 91.7, df = 11, $P = 10^{-14}$	
Risk Factor	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Dexamethasone Baseline: Drug not given	0.58 (0.38, 0.89)	0.013	0.56 (0.36, 0.87)	0.010
Intraoperative transfusion Baseline: No transfusion	1.21 (1.10, 1.32) Per unit transfused	10^{-4}	1.21 (1.12, 1.32) Per unit transfused	10^{-5}
Perioperative epidural analgesia Baseline: Used	1.94 (1.07, 3.52)	0.029	1.86 (1.16, 2.98)	0.010
Tumor stage Baseline: ia	12.78 (2.45, 66.78) stage ia *vs.* stage iv (ordered factor)	0.003	13.36 (3.35, 53.22) stage ia *vs.* stage iv (ordered factor)	0.0002
Tumor histologic grade Baseline: g1	3.78 (1.48, 9.69) grade g1 *vs.* grade g3 (ordered factor)	0.006	3.60 (1.47, 8.82) grade g1 *vs.* grade g3 (ordered factor)	0.005
Adjuvant chemotherapy Baseline: Not given	0.54 (0.33, 0.88)	0.01	0.54 (0.33, 0.89	0.015
Margin involvement Baseline: Involved	0.92 (0.51, 1.65)	0.77	NA	NA
Tumor maximum size (per cm)	0.99 (0.85, 1.15)	0.89	NA	NA
Intraoperative fentanyl equivalents (per mcg)	1.00 (1.00, 1.00)	0.51	NA	NA
Intraoperative morphine equivalents (per mg)	1.02 (0.96, 1.08)	0.54	NA	NA

CI = confidence interval; NA = data missing.

P values of the coefficients in Model 2 (table 3) at an alpha of 0.05. All coefficients were still significant. Since the number of null-hypotheses rejected whose *P* values being tested by the FDR procedure was six, less than one ($6 \times 0.05 = 0.3$) falsely rejected null hypotheses is to be expected among the six null hypotheses rejected.

Predicted median survival using Model 2 (table 3) was estimated with the four combinations of dexamethasone (yes, no) and perioperative epidural analgesia (yes, no). The other four covariates were set to their median values. The point estimates (medians) show the joint effect of the administration of dexamethasone and the use of postoperative epidural analgesia to prolong survival (table 4). While the 95% CI are wide, a significant clinical effect is evident. Administering dexamethasone and using epidural analgesia would increase median survival from 370 to 651 days compared to not receiving dexamethasone and not receiving epidural analgesia.

Discussion

In 2000, Hanahan and Weinberg[18] described the original six hallmarks of cancer. These included evasion of apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, tissue invasion and metastasis, limitless replicative potential, and sustained angiogenesis. Over a decade later in 2011, these authors added emerging hallmarks and enabling characteristics of cancer, which now include deregulating cellular energetics, avoiding immune destruction, tumor-promoting inflammation, and genome instability and mutation.[19] Data from animal studies suggest that immune system components such as cytotoxic T-lymphocytes, natural killer cells, macrophages, and dendritic cells are responsible for controlling tumor cell growth and micrometastases.[20] Immunosuppression caused by surgical procedures, stress, and anxiety creates a window for tumor cells to avoid immune destruction. Cancer patients who undergo surgical resection as part of their treatment find themselves at increased risk of disseminated disease.[21]

Multiple retrospective analyses have shown relationships between perioperative management and cancer outcomes. To our knowledge, this is the first reported association between

Table 4. Model-based Predicted Survival for Combinations of Values of Dexamethasone (Yes/No) and Epidural Analgesia (Yes/No)

Covariate Pairing	Median Survival (days) Median (95% CI)
Dexamethasone: yes Epidural analgesia: yes	651 (520, 1,231)
Dexamethasone: yes Epidural analgesia: no	471 (370, 1,346)
Dexamethasone: no Epidural analgesia: yes	479 (423, 680)
Dexamethasone: no Epidural analgesia: no	370 (267, 620)

Other covariates fixed at median values: intraoperative transfusion = 0 units; tumor stage = iib; tumor histologic grade = g2; postoperative chemotherapy = not given.

CI = confidence interval.

intraoperative dexamethasone administration and improved survival in human pancreatic adenocarcinoma patients. Rhim *et al.*[14] described decreased dissemination of pancreatic adenocarcinoma with dexamethasone administration in a mouse model. Their proposed mechanism was a decrease in inflammation causing a reduction in epithelial-to-mesenchymal transition. When a pancreatic epithelial cell is able to maintain a mesenchymal phenotype, it is capable of exhibiting properties of a stem cell. If that cell is then disseminated and seeded to distant sites such as the liver, it is able to multiply and grow.[14] Thus, it is plausible that inflammation is necessary for pancreatic cancer progression, in that it aids epithelial-to-mesenchymal transition and dissemination. Antiinflammatory interventions such as ketorolac, statins, a healthy diet, omega-3 fatty acids, and others have been associated with improved outcomes in cancer patients.[7,22–24] It is possible that the antiinflammatory effects of dexamethasone contributed to the noted association with increased survival in our study. The association seen between the administration of dexamethasone and survival in our analyses support the findings described by Rhim *et al.*[14] We propose that the mechanisms described in their mouse model could be responsible for our observations. Due to our limited sample size, there is uncertainty regarding the magnitude of the dose effect of dexamethasone.

We initially included dexamethasone as a variable, because we were concerned that its immunosuppressive effects could decrease survival. Previous evidence suggests that an attenuated immune response from surgical stress may be responsible for increased tumor growth.[25] A suppressed immune response from steroids could theoretically be harmful to patients with pancreatic cancer. If dexamethasone does have immunosuppressive effects, it appears as though its antiinflammatory properties may have a greater effect on survival. Others have noted no effects on cancer recurrence; De Oliveira *et al.*[26] reported that there was no augmentation of ovarian cancer recurrence with perioperative dexamethasone.

The use of a perioperative epidural was associated with increased survival. Multiple retrospective studies have shown associations between improved survival and use of regional analgesia,[5,27–29] while others have failed to show such associations.[30–32] Opioid reduction, sparing of volatile anesthetics, attenuation of stress response, and a decrease in the inflammatory response have all been postulated as possible mechanisms for the improved survival noted with regional anesthesia.[25,33] In our study, having an epidural did not seem to have a significant effect on the dose of opioid used perioperatively. Nevertheless, an association between the use of epidural anesthesia during primary pancreatic cancer surgery and prolonged survival was observed. We believe that the reason for minimal differences in opioid administration was because the epidural was usually dosed near the end of surgery. Thus, opioids were administered throughout the case in a similar fashion. Local anesthetics have been shown to have antiinflammatory effects.[34] Amide local anesthetics have also been shown to have anti-proliferative effects on mesenchymal stem cells.[35] Although our dataset was unable to assess the mechanism by which epidural use was associated with increased survival, these antiinflammatory and antiproliferative effects could be involved.

Our results were consistent with previously identified associations between perioperative blood transfusions and decreased survival. Intraoperative transfusions were associated with significantly decreased survival. A mechanism for this association cannot be identified in the available dataset; however, immunosuppression has been suggested in other studies.[12] It is also possible that the need for a blood transfusion was a surrogate marker for any other undefined risk factor that may account for the difference in survival. As anticipated, an association between poor tumor stage/histologic grade and decreased survival was confirmed in our dataset.

We acknowledge the potential limitations brought on by a retrospective study design. Unobserved confounding bias may be responsible for some or all of the findings. One hundred and forty-five patients is a relatively small cohort from which to conduct a multivariable analysis. This sample size was one of convenience, using all available patients from 2001 to 2012 at our institution. We recognize that a larger percentage of patients in the dexamethasone group received postoperative adjuvant chemotherapy. This may have influenced our findings. All of the variables included and analyzed in the study could influence survival in cancer patients; however, unrecognized bias is a common occurrence in retrospective studies and one or more important variables could have gone unnoticed. Despite such limitations, our dexamethasone findings are in line with published animal data. Our findings regarding improved outcomes with use of epidural anesthesia are consistent with some previously published studies. Again, the limitations of a retrospective study restrict our ability to determine a mechanism for our findings and the wide CIs seen in our statistical analyses suggest that the magnitude of the survival effect is uncertain.

Investigators at institutions with similar pancreatic cancer data resources should consider observational survival analyses on the effect of dexamethasone. Assuming similar conditions (overall mortality about 70%, approximately equal proportions receiving/not receiving dexamethasone), a sample of 170 patients will have 80% power to identify a HR of 0.6 favoring dexamethasone. Prospective randomized clinical trials are warranted to confirm or refute these hypotheses; namely, that epidural anesthesia and single-dose IV dexamethasone during primary pancreatic carcinoma resection improves survival. Considering the range of HRs (0.4, 0.5, 0.6, 0.7, 0.8, 0.9) for the effect of dexamethasone on survival, the total sample size necessary for such a trial will vary widely according to the postulated true HR. For HRs of 0.4 to 0.6, a trial of 300 patients will have statistical power much greater than 80%. For smaller effect sizes

(HR = 0.8 or 0.9), a trial of 3,000 to 4,000 patients will be necessary.

Given the significant morbidity and mortality associated with pancreatic adenocarcinoma, the possibility of increasing survival by optimizing perioperative management would have significant implications.

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Competing Interests

The authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From Paris to Tunis: Bellon Advertising Xylocaine

From the Parisian suburb of Neuilly: the Roger Bellon Laboratory used a 4-Franc stamp to send this postcard advertising (*low*) "Xylocaïne/Anesthésie locale/Injections thérapeutiques." *From 33 miles southeast of Paris:* the Palace of Fontainebleau, the royal or imperial residence of French leaders from King Louis VII to Napoleon III, was photographed (*high*) to grace the front of this postcard. *From 922 miles southeast of Paris:* the addressees of this postcard, the Doctors Coursieres, conducted their medical practice in Montfleury, a district in Tunis, the Tunisian capital. A French protectorate since 1881, Tunisia would gain its independence in 1956. Marketed after World War II, the local anesthetic Xylocaine remains popular to this day—at least in its generic form of lidocaine—in Tunisia and around the world. (Copyright © the American Society of Anesthesiologists, Inc.)

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