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A Comparison of the Effects of Epidural Analgesia Versus Traditional Pain Management on Outcomes After Gastric Cancer Resection: A Population-Based Study

Kenneth C. Cummings III, MD, MS[†], Meatal Patel, MPH[‡], Phyo Than Htoo, MD, MPH[‡], Paul M. Bakaki, MD, PhD[‡], Linda C. Cummings, MD, MS[§], and Siran Koroukian, PhD[#]

[†]Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH

[‡]Case Western Reserve University, Cleveland, OH

[§]Division of Gastroenterology and Liver Disease, University Hospitals Case Medical Center, Cleveland, OH

[#]Department of Epidemiology and Biostatistics, School of Medicine, and Case Comprehensive Cancer Center, Population Health and Outcomes Research Core, Clinical and Translational Science Collaborative, Case Western Reserve University, Cleveland, OH

Abstract

Background and Objectives—Epidural analgesia may increase survival after cancer surgery by reducing recurrence. This population-based study compared survival and treated recurrence after gastric cancer resection between patients receiving epidurals and those who did not.

Methods—We used the linked federal Surveillance, Epidemiology, and End Results (SEER) Program/Medicare database to identify patients aged ≥66 with nonmetastatic gastric carcinoma diagnosed 1996–2005 who underwent resection. Exclusions included diagnosis at autopsy, no Medicare Part B, familial cancer syndrome, emergency surgery, and laparoscopic procedures. Epidurals were identified by CPT codes.

Treated recurrence was defined as chemotherapy ≥16 months and/or radiation ≥12 months after surgery. Recurrence was compared by conditional logistic regression. Survival was compared via marginal Cox proportional hazards regression.

Results—We identified 2745 patients, 766 of whom had epidural codes. Patients receiving epidurals were more likely to have regional disease, be white, and live in areas with relatively high socioeconomic status. Overall treated recurrence was 25.6% (27.5% epidural and 24.9% non-

Corresponding Author: Kenneth C. Cummings III, MD, MS, Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave, E-30, Cleveland, OH 44195, cummink2@ccf.org.

Departmental Attribution:

Anesthesiology Institute, Cleveland Clinic, Cleveland, OH

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epidural). In the adjusted logistic regression, there was no difference in recurrence (odds ratio [OR] 1.40, 95% CI 0.96 to 2.05).

Median survival did not differ: 28.1 months (95% CI 24.8 to 32.3) in the epidural versus 27.4 months (95% CI 24.8 to 30.0) in the non-epidural groups. The marginal Cox models showed no association between epidural use and mortality (adjusted HR 0.93, 95% CI 0.84 to 1.03).

Conclusions—There was no difference between groups regarding treated recurrence or survival. Whether this is true or simply a result of insufficient power is unclear. Prospective studies are needed to provide stronger evidence.

INTRODUCTION

Although much less common than other malignancies, gastric cancer carries a grave prognosis. In 2013, the American Cancer Society estimated a total of 21,600 people would be diagnosed with gastric cancer and an estimated 10,990 patients would die from it.¹ A key determinant of outcome in patients operated for gastric cancer is local or regional recurrence,² with reported rates after resection with curative intent of 21% to 49%.^{3–4} Even with optimal surgical technique, tumor surgery may release tumor cells into the lymphatics and vasculature, and a large fraction of patients already harbor remote foci of tumor cells at the time of surgery.^{5–6}

Whether these factors result in clinically apparent disease depends largely on the balance between immune activity (tumor surveillance) and the tumor's ability to invade, proliferate, and promote angiogenesis.⁷ Realistically, the immune system and other host defenses frequently fail to eliminate minimal residual disease. As a result, local recurrence and metastatic disease remain common after gastric cancer surgery.

Several perioperative factors have been found to affect the balance between metastasis and tumor surveillance in the perioperative period.^{5–6,8–11} General anesthesia,^{12–13} opioid analgesics,^{14–15} and allogeneic blood transfusion, which is often necessary in large surgical procedures, are known to be immunosuppressive. Regional or neuraxial anesthetic techniques, even when combined with general anesthesia, may suppress immune function less than opioid analgesia^{15–16} by reducing the surgical stress response and significantly reducing opioid exposure. For example, regional anesthetic techniques have been associated with lower recurrence rates of breast and prostate cancers.^{17–18} However, results for colon cancer vary,^{19–21} while the literature is silent on gastric cancer.

The effect of neuraxial anesthetic techniques on survival after surgery has also been heavily debated. Although original reports suggested a survival benefit of neuraxial anesthesia/analgesia for different types of surgery,²² published results for survival after colorectal cancer surgery have differed, with some studies demonstrating a survival benefit^{19,23–24} and others finding none.²¹ While cancer recurrence will impact survival to a large extent, neuraxial anesthesia/analgesia may also reduce perioperative cardiac and respiratory events.²²

Although retrospective by nature, administrative databases provide data not easily found outside of large randomized clinical trials.²⁵ In particular, Medicare claims provide a large

volume of patient encounters for research. Using the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we compared overall survival and cancer recurrence rates between patients who did or did not receive epidural anesthesia and/or analgesia for open resection of nonmetastatic gastric cancer. Our hypotheses were that epidural anesthesia and/or analgesia are associated with (1) reduced cancer recurrence after gastric cancer resection and (2) improved all-cause mortality after surgery.

METHODS

This study was approved by the National Cancer Institute and the Institutional Review Boards of Cleveland Clinic and University Hospitals Case Medical Center, Cleveland, Ohio.

Data Sources

The SEER tumor registry of the National Cancer Institute tracks cancer incidence in a set of cancer registries across the United States which currently encompass over a quarter of the U.S. population. Data collected include patient demographics (age, race, gender, marital status), primary site, prior cancer diagnoses, histology, stage, site specific surgery, and initial course of therapy. Patients in the SEER database who are also enrolled in Medicare can be identified by linking SEER and Medicare data, resulting in a joint database of patients aged ≥ 65 years who were diagnosed with cancer while living in one of the SEER areas. The Patient Entitlement and Diagnosis Summary File (PEDSF) includes data from SEER and Medicare enrollment data. Medicare Part A claims for inpatient hospital care are contained in the Medicare Provider and Analysis Review (MedPAR) file. Medicare Part B claims for physician services and outpatient services are available in the Outpatient Standard Analytical File and the National Claims History files. International Classification of Diseases, 9th Edition-Clinical Modification (ICD-9-CM) and Current Procedural Terminology, 4th Edition (CPT-4) procedure codes can be used to identify procedures from Medicare hospital inpatient claims (MedPAR) and physician-supplier claims. The SEER-Medicare database and its use in cancer research have been described previously.²⁶

Study Population

Patients aged ≥ 66 years diagnosed with incident non-metastatic gastric carcinoma between 1996 and 2005 (identified from PEDSF) who underwent gastrectomy (identified from MedPAR) were included. Cases with anatomical site codes for fundus, body, gastric antrum, pylorus, lesser and greater curvature, overlapping lesion, and stomach were included. The most recent available Medicare data were from 2009, providing at least 4 years of follow-up for cancer recurrence. Patients aged 66 years and older were included to allow for available claims to assess comorbid conditions 1 year prior to gastric cancer diagnosis. Using SEER Summary Stage, patients who presented with localized or regional stage disease and underwent gastrectomy within 6 months of diagnosis as indicated in Medicare claims data were included.

The following cases (identified in PEDSF or from Medicare data) were excluded: carcinoma in situ, metastatic disease, or unstaged cancers; prior diagnosis of cancer; cancer diagnosed on autopsy or death certificate only; eligibility for Medicare on the basis of end stage renal

disease or disability; and patients with Medicare Health Maintenance Organization enrollment or without both Medicare Parts A and B coverage, due to lack of claims data needed for the analysis. Patients undergoing laparoscopic gastrectomy were excluded due to low likelihood of epidural catheter placement. Patients with diagnoses suggesting urgent or emergent procedures according to the method of Diggs et al²⁷ were excluded. Finally, patients who developed an unrelated second malignancy (indicated in PEDSF) after gastric cancer diagnosis were excluded.

Using these criteria, 2 cohorts were identified. To ensure complete claims history, the cohort for assessment of survival consisted of patients enrolled in Medicare Part A and B within 1 year prior to cancer diagnosis until death or 8 months after diagnosis, whichever came first, in order to capture perioperative data and complications. The cohort for assessment of cancer recurrence consisted of patients enrolled in Medicare Part A and B within 1 year prior to cancer diagnosis until death or 4 years after diagnosis who survived at least 12 months after surgery. Figure 1 details the application of the exclusion criteria.

Measures

Exposure—CPT codes for placement of thoracic and lumbar epidural catheters (62318 and 62319, respectively) and daily hospital management of an epidural infusion (01996) were identified from the Standard Analytical File and National Claims History file. Epidural codes were identified ranging from one week prior to and after surgery. These codes have been previously been used successfully in Medicare database research.^{19,28–30} Cases with codes for epidural placement or daily management were considered to be in the epidural group.

Outcome—All-cause mortality after cancer resection was determined by the Medicare date of death as documented in PEDSF. The secondary outcome was treated gastric cancer recurrence, which was defined within a 4-year window after surgery as an ICD-9 metastasis code (197.5) or receipt of chemotherapy 16 months after resection and/or radiation therapy 12 months after resection.^{31–32} This approach has been validated using SEER-Medicare data in a previous study.³³

Covariates—From PEDSF, patient-level demographic and clinical data were collected including age, gender, race, marital status, SEER site, year of diagnosis, anatomical site, and cancer stage at diagnosis. Census tract level variables (urban/rural residence, median income, and percent of residents with at least a high school diploma) were used as a proxy for socioeconomic status. Blood transfusions were noted from MedPAR claims.

Comorbid conditions were identified using ICD-9-CM codes from MedPAR, Outpatient, and physician-supplier claims to calculate a comorbidity score modified from the Deyo adaptation of the Charlson comorbidity index³⁴ as recommended by the National Cancer Institute.* Klabunde's 30-day rule out algorithm was applied to incorporate comorbid conditions from outpatient claims.³⁵

*<http://healthservices.cancer.gov/seermedicare/program/comorbidity.html>, last accessed 10/10/2011

Gastrectomy—We examined MedPAR and physician-supplier claims for surgical procedure codes. We used the following ICD-9-CM procedure codes for gastrectomy: proximal gastrectomy (43.5), partial gastrectomy with anastomosis to duodenum (43.6), partial gastrectomy with anastomosis to jejunum (43.7), other partial gastrectomy (43.8x), and total gastrectomy (43.9x). Additionally, the following CPT codes were evaluated: total gastrectomy (43620-22) and partial distal gastrectomy (43631-43634). The use of an ICD-9-CM diagnosis code of V64.4 (conversion of a laparoscopic procedure to open) in conjunction with procedure codes for gastrectomy in the absence of procedure codes for laparoscopy (54.21, 45.81) was considered to be a laparoscopic procedure that was converted to open. These patients were excluded from the analytic cohort. If a patient had a gastrectomy and the codes for laparoscopy were not present, then the patient was assumed to have had an open gastrectomy.

Complications—Medicare claims data from surgery date until 30 days after surgery were evaluated for perioperative complications. Complications included ICD-9 or CPT-4 codes for retrieval of retained foreign body, accidental puncture or laceration, incision of abdominal wall, management of postoperative shock/hemorrhage, management of abdominal infection, repair of an organ injury/laceration, reoperative laparotomy, management of wound complication, management of fistula, and management of bowel obstruction.³⁶

Statistical Analysis

Patient characteristics were compared between the epidural anesthesia and/or analgesia group and the non-epidural group. For categorical variables, Pearson's chi square test was used. For continuous variables, medians with interquartile ranges are presented. Wilcoxon rank sum tests were used to compare the groups.

Survival time was measured from the date of gastrectomy to death or last follow-up through December 31, 2009, indicated as censor. Kaplan-Meier survival curves were generated. Survival times between treatment groups (epidural versus no epidural) were compared using the log-rank test. For multivariate survival analysis, a marginal Cox model was constructed given the nature of the hospital clustered data. This method yields a stronger estimate of covariate effects. A robust sandwich estimate was implemented in the model.³⁷ As a confirmatory analysis, using logistic regression, a propensity score was generated to predict the probability of the use of epidural anesthesia using the same covariates. The propensity score was then incorporated into the survival models as a continuous covariate.

In the analysis of the recurrence cohort, a conditional logistic regression was constructed to predict the likelihood of treated cancer recurrence, controlling for hospital effect.

Finally, in an effort to determine what treatment effect would be detectable given these results, an exploratory post hoc power analysis was conducted using the observed cohort size and proportion of epidural use.

Analysis was conducted with SAS software version 9.3 (SAS Institute, Cary, NC). All comparisons used 2-sided tests with *P* values < 0.05 considered significant.

RESULTS

Patient Selection

Using the inclusion and exclusion criteria described, we identified a cohort of 2745 patients, of whom 27.9% (n=766) had epidurals. The cohort for analysis of cancer recurrence comprised 1882 patients, of whom 28.8% (n=542) had epidurals at the time of resection.

Patient Characteristics

There were a number of differences between the 2 groups (Table 1). Patients who received epidurals were more likely to be white and live in areas with higher median income and education. Epidural use was also more common in the Midwest SEER region and increased slightly over the study interval. Epidural use differed by tumor extent as well, with patients receiving epidurals more likely to have regional stage disease. Epidural use did not differ significantly by tumor location in the stomach. Patients with epidurals were also slightly more likely to have surgical complications.

Association Between Epidural use and Overall Survival

Median survival in the epidural group was 28.1 months (95% CI 24.8 – 32.3); in the non-epidural group, median survival was 27.4 months (95% CI 24.8 – 30.0). Figure 2 shows Kaplan-Meier survival curves for the two groups; the curves were not significantly different (log-rank test P value= 0.54). Table 2 presents both the unadjusted and adjusted marginal Cox models. Model checking was based on cumulative sums of Martingale based residuals and the models had a good fit. Adjusting for multiple patient characteristics, there was no significant association between epidural use and improved overall survival (adjusted hazard ratio (HR) = 0.93, 95%CI 0.84 – 1.03; P =0.17). Covariates independently associated with increased mortality hazard include increasing age, male gender, surgical complications, increasing Charlson score, increasing tumor grade and stage, tumor location, and blood transfusion. For transfusion, the adjusted hazard ratio for mortality was 1.18, 95% CI 1.02 to 1.36; P value = 0.026.

As a confirmatory analysis, we used the same covariates used in the adjusted Cox model (omitting blood transfusion and postoperative complications because they would not predict the use of epidural analgesia) to create a logistic regression model predicting a propensity score (likelihood of receiving an epidural). We then incorporated this propensity score as a covariate in the adjusted Cox proportional hazards analysis (Table 2, Models 2A, 2B, and 2C). Adjusting for the propensity score as a continuous variable, the results did not change significantly (HR=0.95, 95% CI 0.85 – 1.07; P =0.32).

Association Between Epidural Use and Treated Cancer Recurrence

Overall 4-year treated recurrence was 25.6% (27.5% in the epidural group and 24.9% in the non-epidural group. In the unadjusted conditional logistic regression (Table 3), there was no significant association between epidural use and cancer recurrence (OR = 1.38, 95%CI 0.98 – 1.95; P value = 0.06). There were, however, a number of significant predictors of treated recurrence: male gender, increasing Charlson score, higher tumor grade, increasing stage, residence in an area with higher education, and later year of diagnosis were associated with

higher odds of recurrence. Adjusting for these and other demographic and clinical covariates did not appreciably change the result describing the association between epidural use and treated tumor recurrence (OR = 1.40, 95% CI 0.96 –2.05; *P* value = 0.08).

Post-Hoc Power Analysis

Assuming the worst case of 766 per group with 24.9% treated recurrence in the non-epidural group, this analysis yielded 86% power to detect a 7% absolute difference in treated recurrence and 93% power to detect an 8% difference. These relatively small differences suggest adequate statistical power (within the limitations of a post-hoc analysis).

DISCUSSION

Given the preclinical and observational data supporting immune function as a protective factor against cancer spread, it is reasonable to study whether interventions aimed at reducing exposure to immunosuppressive factors would improve patient outcomes after cancer resection. This has, however, been difficult to demonstrate with available data for gastric cancer. Unlike prior observational studies evaluating colorectal,¹⁹ breast,¹⁷ and prostate¹⁸ cancer, this analysis failed to find an association between epidural use and either treated recurrence or differences in mortality after gastrectomy.

There is literature investigating other malignancies that is consistent with our findings. Gottschalk et al. analyzed 669 patients undergoing colorectal cancer resection and found no overall association between epidural analgesia and recurrence risk, although their study was limited by length of follow-up.²⁰ Myles et al²¹ evaluated recurrence of multiple abdominal cancers in groups randomized to either epidural or systemic analgesia. They found no significant difference in overall recurrence between the groups (combining all the tumors), but the study had insufficient power to detect an effect on any one malignancy.

Such disparate results highlight the difficulties facing investigators in this field. Differences in tumors, surgical techniques and skill, and patient populations, as well as challenges in defining recurrence and difficulty with long-term follow-up all hamper the ability to draw firm conclusions. Clinicians will need to wait for the results of ongoing clinical trials for more reliable information.

One interesting observation that can be made about these results is to note the direction of association. A completely unadjusted odds ratio for treated recurrence from our data is 1.15 (chi square *P* value = 0.24). In the unadjusted conditional logistic regression model, the odds ratio for recurrence is 1.38 (*P* = 0.06), strongly suggestive of an association. This discrepancy arises from the fact that the regression model includes clustering due to hospitals. Why might this be so? One plausible explanation is that patients at high-volume academic medical centers would be more likely to receive epidural analgesia and would also probably be more likely to have aggressive or unusual disease presentation. They may potentially also have been treated more aggressively after gastrectomy which would appear in this analysis as a recurrence event. Without more patient- and hospital-specific data, this remains hypothetical and is an avenue for further research. Of note, we observed a similar

phenomenon in a previous study evaluating colorectal cancer recurrence that used a similar design.¹⁹

Of note, we found a significant association between perioperative blood transfusion and an increased mortality hazard. This is consistent with the recognized negative effects of blood transfusion. In colon cancer patients, transfusion has previously been associated with increased odds of recurrence after surgery.^{19,38} In a wider surgical population, Glance et al found an association between blood transfusion and an increase in multiple perioperative complications, including death.³⁹ Given the observational nature of the present study, however, it is still unknown if transfusion causes worse outcomes or is simply a marker of a poor clinical course.

There are important limitations to this analysis. It suffers from the same weaknesses inherent to all observational studies, including susceptibility to bias and confounding. Because gastric cancer is relatively uncommon (and we had to exclude many patients to generate our analytic cohort), our study may be underpowered to detect a true difference between groups. Alternatively, our results may be explained by unmeasured confounders or selection bias. The post hoc power analysis would support this argument, but these analyses must be interpreted cautiously. We used propensity scores in an attempt to adjust for potential selection bias in treatment assignment, but we were limited to the available covariates. Because propensity scores only balance groups on known variables, unmeasured confounders may still remain.

Additionally, this database, because it is based on Medicare claims, contains limited clinical data. The timing of epidural use (preoperative, intraoperative, or only for a few days postoperatively) and the epidural failure rate are also unclear from this database. Without any other means of identifying epidural use in this database, some level of misclassification will be inevitable. The misclassification, however, should bias toward a null result. Additionally, the non-epidural group may have received a variety of analgesic modalities (eg, bolus opioids, intrathecal morphine, patient-controlled analgesia, local infiltration) which would increase the heterogeneity of the group.

Finally, the database does not have a variable indicating cancer recurrence. Therefore, we were not able to assess disease-free survival. Using subsequent treatments as proxies for recurrence may lead to cases of untreated recurrence going undetected, which could bias the result of the recurrence analysis. This is likely, as our detected rate of treated recurrence (25.6%) is on the lower end of the spectrum of reported recurrence rates. Also, due to the limitations of the database, we may have omitted clinically significant covariates from our statistical models and were unable to directly examine nonsurgical complications (such as cardiac events). Finally, our dataset was limited to individuals aged ≥ 66 years.

This study, however, has several strengths worth mentioning. The SEER-Medicare database is large, provides detailed tumor information, and is maintained by the National Cancer Institute. The data quality is very good and provides information from across the United States. This combination of clinical data with Medicare claims allows many questions to be addressed which would be impractical to study prospectively.

In conclusion, this population-based cohort study suggests that epidural anesthesia and/or analgesia is not associated with reduced treated recurrence or improved survival in patients with local or regional stage gastric cancer undergoing resection. Prospective studies are still needed.

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Figure 1.
Application of exclusion criteria

Figure 2.
Kaplan-Meier survival curves for patients with and without epidural billing codes

Table 1

Patient Characteristics by Type of Pain Management

Characteristics	Total sample (n=2745)	Traditional Pain Management (n=1979)	Epidural Anesthesia and/or Analgesia (n=766)	P Value
Age at diagnosis (95% CI)	76.8 (72.3, 82.2)	76.9 (72.5, 82.3)	76.5 (72.0, 81.8)	0.0709
Categorical age				0.3338
66–69	397 (14.46)	273 (13.79)	124 (16.19)	
70–74	683 (24.88)	488 (24.66)	195 (25.46)	
75–79	736 (26.81)	531 (26.83)	205 (26.76)	
80–84	555 (20.22)	405 (20.46)	150 (19.58)	
85+	374 (13.62)	282 (14.25)	92 (12.01)	
Gender				0.1214
Female	1323 (48.20)	972 (49.12)	351 (45.82)	
Male	1422 (51.80)	1007 (50.88)	415 (54.18)	
Race				<0.0001
White	1534 (55.88)	1020 (51.54)	514 (67.10)	
Black	288 (10.49)	219 (11.07)	69 (9.01)	
Other	923 (33.62)	740 (37.39)	183 (23.89)	
Marital status				0.3406
Married	1509 (54.97)	1071 (54.12)	438 (57.18)	
Not married	1157 (42.15)	849 (42.90)	308 (40.21)	
Unknown	79 (2.88)	59 (2.98)	20 (2.61)	
Education* (95% CI)	81.0 (69.8, 89.1)	79.6 (67.5, 88.8)	83.6 (74.4, 90.0)	<0.0001
Income [†]	42454 (31067, 57433)	41895 (30361, 57280)	44647 (32850, 59290)	0.0017
Residence				0.4918
Metropolitan	2439 (88.85)	1766 (89.24)	673 (87.86)	
Urban	>270 (>9.8)	190 (9.60)	85 (11.10)	
Rural	**	**	**	
SEER region				<0.0001
Midwest	371 (13.52)	180 (9.10)	191 (24.93)	
Northeast	569 (20.73)	423 (21.37)	146 (19.06)	
South	329 (11.99)	250 (12.63)	79 (10.31)	
West	1476 (53.77)	1126 (56.90)	350 (45.69)	
Charlson Index				0.0626
0	1970 (71.77)	1405 (71.00)	565 (73.76)	
1	505 (18.40)	361 (18.24)	144 (18.80)	
2	164 (5.97)	127 (6.42)	37 (4.83)	

Characteristics	Total sample (n=2745)	Traditional Pain Management (n=1979)	Epidural Anesthesia and/or Analgesia (n=766)	P Value
3+	106 (3.86)	86 (4.35)	20 (2.61)	
Tumor differentiation				0.1109
Well	142 (5.17)	115 (5.81)	27 (3.52)	
Moderately	849 (30.93)	610 (30.82)	239 (31.20)	
Poorly	1576 (57.41)	1125 (56.85)	451 (58.88)	
Others/Unknown	178 (6.48)	129 (6.52)	49 (6.40)	
Blood transfusion				0.9363
No	2370 (86.34)	1708 (86.31)	662 (86.42)	
Yes	375 (13.66)	271 (13.69)	104 (13.58)	
Stage				0.0085
Local	999 (36.39)	750 (37.90)	249 (32.51)	
Regional	1746 (63.61)	1229 (62.10)	517 (67.49)	
Year of diagnosis				0.0082
1996	177 (6.45)	121 (6.11)	56 (7.31)	
1997	189 (6.89)	120 (6.06)	69 (9.01)	
1998	174 (6.34)	121 (6.11)	53 (6.92)	
1999	201 (7.32)	130 (6.57)	71 (9.27)	
2000	319 (11.62)	236 (11.93)	83 (10.84)	
2001	349 (12.71)	257 (12.99)	92 (12.01)	
2002	341 (12.42)	253 (12.78)	88 (11.49)	
2003	306 (11.15)	237 (11.98)	69 (9.01)	
2004	368 (13.41)	262 (13.24)	106 (13.84)	
2005	321 (11.69)	242 (12.23)	79 (10.31)	
Cancer site				0.1086
Fundus	108 (3.93)	73 (3.69)	35 (4.57)	
Body	303 (11.04)	219 (11.07)	84 (10.97)	
Antrum	966 (35.19)	727 (36.74)	239 (31.20)	
Pylorus	175 (6.38)	126 (6.37)	49 (6.40)	
Lesser curvature	449 (16.36)	315 (15.92)	134 (17.49)	
Greater curvature	191 (6.96)	126 (6.37)	65 (8.49)	
Overlapping lesion	226 (8.23)	155 (7.83)	71 (9.27)	
Stomach, NOS	327 (11.91)	238 (12.03)	89 (11.62)	
Complications				0.0482
No	2449 (89.22)	1780 (89.94)	669 (87.34)	
Yes	296 (10.78)	199 (10.06)	97 (12.66)	

* Percent of residents in census tract with at least a high school education

** Counts < 11 masked (and one adjacent cell with reduced precision) due to National Cancer Institute privacy requirements

[†]Median income (U.S. dollars) of census tract

Table 2

Association Between Type of Pain Management and All-Cause Mortality

Models*	Hazard Ratio	95% CI	P Value
Model 1A	0.97	(0.87, 1.09)	0.65
Model 1B	0.93	(0.84, 1.03)	0.17
Model 2A	0.95	(0.85, 1.07)	0.39
Model 2B	0.95	(0.85, 1.07)	0.36
Model 2C	0.94	(0.84, 1.06)	0.26

* Marginal clustered survival models based on robust sandwich estimate

Model 1A – Epidural alone (unadjusted)

Model 1B – Epidural adjusted by age, gender, race, marital status, education, median income, year of diagnosis, Charlson score, tumor grade, stage, blood transfusion, cancer site and surgical complications.

Model 2A – Epidural adjusted by propensity score

Model 2B – Epidural adjusted by propensity score and blood transfusion

Model 2C – Epidural adjusted by propensity score and surgical complications

(Propensity score model includes age, gender, race, marital status, education, median income, year of diagnosis, Charlson score, tumor grade, stage, cancer site, SEER regions and residence type. Transfusion and surgical complications were not included because they would not logically predict the use of epidural analgesia.)

Table 3

Association Between Type of Pain Management and Tumor Recurrence

Models*	Odds Ratio	95% CI	P Value
Model 1A	1.38	(0.98, 1.95)	0.06
Model 1B	1.40	(0.96, 2.05)	0.08
Model 1C	1.37	(0.97, 1.93)	0.07
Model 1D	1.38	(0.98, 1.94)	0.07

* Conditional logistic regression models adjusting for hospital effect.

Model 1A – Epidural alone (unadjusted)

Model 1B – Epidural adjusted by age, sex, race, marital status, education, median income, year of diagnosis, blood transfusion, Charlson score, tumor grade, stage, cancer site and surgical complications.

Model 1C – Epidural adjusted by surgical complications only (Surgical complication is not predictive of recurrence in the adjusted model)

Model 1D – Epidural adjusted by blood transfusion only (Blood transfusion is not predictive of recurrence in the adjusted model).