A Comparison of Epidural Analgesia and Traditional Pain Management Effects on Survival and Cancer Recurrence after Colectomy

A Population-based Study

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ABSTRACT

Background: Cancer recurrence after surgery may be affected by immunosuppressive factors such as surgical stress, anesthetic drugs, and opioids. By limiting exposure to these, epidural analgesia may enhance tumor surveillance. This study compared survival and cancer recurrence rates for resection of colorectal cancer between patients who received perioperative epidurals and those who did not.

Methods: The linked Medicare-Surveillance, Epidemiology, and End Results database was used to identify patients ages 66 yr or older with nonmetastatic colorectal cancer diagnosed between 1996 and 2005 who underwent open colectomy. Recurrence was defined as chemotherapy 16 months or more after surgery and/or radiation 12 months or more after surgery. Patients were followed for at least 4 yr. To account for hospital effects, overall survival was estimated *via* marginal Cox regression. Recurrence was estimated by conditional logistic regression.

Results: A cohort of 42,151 patients, of whom 22.9% (n = 9,670) had epidurals at the time of resection, was identified. 5-yr survival was 61% in the epidural group and 55% in the nonepidural group. There was a significant association between epidural use and improved survival (adjusted Cox model hazard ratio = 0.91, 95% CI = [0.87, 0.94]). Adjusting for covariates, there was no significant reduction of recurrence in the epidural group (odds ratio = 1.05, 95% CI = [0.95, 1.15]). Several covariates, including blood transfusion, were predictive of mortality and cancer recurrence.

Conclusion: This large cohort study found that epidural use is associated with improved survival in patients with nonmetastatic colorectal cancer undergoing resection but does not support an association between epidural use and decreased cancer recurrence.

What We Already Know about This Topic

- Regional anesthesia likely improves acute postoperative analgesia and recovery after cancer surgery, but whether it affects later metastases or survival is unclear

What This Article Tells Us That Is New

- In a case cohort study of more than 42,000 patients undergoing resection for colon cancer, 5-yr survival was greater in those receiving epidurals at the time of surgery (61% compared with 55%)
- Cancer recurrence, measured as later use of chemotherapy or radiation therapy, did not differ in those receiving epidurals and those who did not

COLORECTAL cancer is the third most common cancer diagnosed in the United States and accounted for approximately 9% of all U.S. cancer deaths in 2010.[1] A major determinant of survival in patients undergoing cancer surgery is recurrence, with rates of 8–25% reported for colorectal cancer.[2] To a large degree, the opposing forces of immune surveillance and a tumor's ability to spread determine whether local recurrence or metastasis occurs.[3–4]

Multiple surgical factors can negatively affect the balance between metastasis and tumor surveillance in the perioperative

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period.[3,5–15] Allogeneic blood transfusion, not uncommon in large abdominal procedures, is also widely recognized as immunosuppressive, as are general anesthesia[16–19] and opioid analgesics.[20–21] By reducing the surgical stress response (if used intraoperatively) and significantly reducing exposure to opioids, regional, or neuraxial anesthetic techniques, even when combined with general anesthesia, may suppress immune function less than opioid analgesia.[21–22] Consistent with this hypothesis, regional anesthetic techniques have been associated with lower recurrence rates of breast and prostate cancers.[23–24] Results for colon cancer, however, are mixed,[25–26] prompting the need for additional (and larger) database analyses as prospective trials are conducted.

In addition to effects on cancer recurrence, the impact of neuraxial analgesia on survival after surgery has been a contentious issue. Although widely believed to improve patient outcomes, survival data are less convincing. Whereas original reports suggested a survival benefit of neuraxial anesthesia/analgesia for different types of surgery,[27] results for survival after colorectal cancer surgery have been mixed, with some analyses showing a survival benefit[28–29] and others finding none.[26] Although cancer recurrence will determine survival to a large extent, other putative mechanisms include a reduction in perioperative cardiac, respiratory, and thromboembolic events.[27]

Although limited by their design, administrative database studies provide insights not easily found outside of large randomized clinical trials.[30] In particular, Medicare claims data provide a large pool of patient encounters for research. Therefore, the objectives of this population-based cohort study were to use the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database to compare overall survival and cancer recurrence rates between patients who did or did not receive epidural anesthesia and/or analgesia for open resection of nonmetastatic colorectal cancer. Our hypotheses were that epidural anesthesia and/or analgesia is associated with reduced cancer recurrence after colorectal cancer resection and improved all-cause mortality after surgery.

Materials and Methods

The protocol utilizing the Medicare-SEER database was approved by Case Comprehensive Cancer Center Institutional Review Board (Cleveland, Ohio) and the National Cancer Institute (Bethesda, Maryland).

Data Sources

The SEER tumor registry provides a population-based source of information about patients with colorectal cancer. This tumor registry is a program of the National Cancer Institute at the National Institutes of Health (Bethesda, Maryland) that tracks cancer incidence in a set of cancer registries in the United States. The SEER program began collecting data in 1973, and currently collects patient-specific information about cancer cases from more than a dozen cancer registries encompassing about 26% of the U.S. population. SEER data include primary site, previous cancer diagnoses, histology, stage, site specific surgery, reasons patients did not undergo surgery, surgery of distant sites, and initial course of therapy. These data are contained in the Patient Entitlement and Diagnosis Summary File (PEDSF).

Patients in the SEER database who are also Medicare beneficiaries can be identified by linking the SEER and Medicare databases, resulting in a joint database that consists of patients aged 65 yr or older who were diagnosed with cancer while living in one of the SEER areas. The linked SEER-Medicare database consists of claims from Medicare beneficiaries, which include nearly all individuals 65 yr old or older. Medicare Part A claims for inpatient hospital care and for home health care and hospice services are contained in the Medicare Provider and Analysis Review (MedPAR) file. Medicare Part B claims are for physician services and outpatient services including hospital outpatient, ambulatory surgical centers, and rural health clinics; some home health; and other medical services, and are available in the Outpatient Standard Analytical File and the National Claims History files. Procedures in the linked SEER-Medicare database can be identified from procedure codes (International Classification of Diseases, 9th Edition (Clinical Modification) [ICD-9-CM] and Current Procedural Terminology, 4th Edition [CPT-4]) from Medicare hospital inpatient claims (MedPAR) and physician-supplier claims. A more detailed discussion of the SEER-Medicare database and its use in cancer research can be found in a review by Warren *et al.*[31]

Study Population

Using PEDSF, we identified a cohort of patients aged 66 yr or older diagnosed with incident nonmetastatic colorectal adenocarcinoma between 1996 and 2005 who underwent colectomy (identified from MedPAR). This provided at least 4 yr of follow-up for cancer recurrence, given that the most recent Medicare data are from 2009. Patients aged 66 yr or older were included to allow for claims to be available to assess comorbidities 1 yr before colorectal cancer diagnosis. Patients who presented with localized or regional stage disease (American Joint Committee on Cancer Stages I, II, and III) according to SEER and underwent colectomy within 6 months of diagnosis as indicated in Medicare claims data were included.

The following exclusion criteria (identified in PEDSF and MedPAR) were applied: carcinoma *in situ*, stage IV 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; Medicare Health Maintenance Organization enrollment because of the potential for incomplete claims; diagnosis of familial adenomatous polyposis; and history of inflammatory bowel disease (Crohn's disease or ulcerative colitis). Patients identified as undergoing laparoscopic procedures were excluded because they would be much less likely to have epidural catheters placed. Patients without both Medicare Parts

A and B coverage were excluded because both inpatient and outpatient claims are needed for the analysis. Patients with admitting diagnoses suggesting urgent or emergent procedures according to the method of Diggs *et al.*[32] were excluded. Finally, patients who subsequently developed an unrelated second malignancy (indicated in PEDSF) were excluded.

Using these criteria, two nested cohorts were defined. The cohort for assessment of overall survival was identified as patients who were enrolled in Medicare part A and B within 1 yr before cancer diagnosis until death or 8 months after diagnosis, whichever came first, in order to allow recording of perioperative data and complications. The recurrence cohort for assessment of cancer recurrence was identified as patients who were enrolled in Medicare part A and B within 1 yr before cancer diagnosis until 4 yr after diagnosis or death who survived at least 12 months after surgery.

Measures

Exposure. The exposure variable was epidural anesthesia and/or analgesia. The CPT codes for placement of thoracic and lumbar epidural catheters (62318 and 62319, respectively, with a possible −59 modifier for postoperative pain) as well as the code for daily hospital management of an epidural infusion (01996) were identified from the Standard Analytical File and National Claims History file because MedPAR does not contain information on epidural placement. Epidural codes were searched perioperatively ranging from 1 week before and after surgery. These codes have been used successfully elsewhere in Medicare database research.[33–35] Either a code for epidural placement or a code for daily management was taken as evidence of epidural use.

Outcome. All-cause mortality after cancer resection was determined by the Medicare date of death (recorded in the PEDSF file). Survival time was measured from date of resection to death or 12/31/2009 if censored. The secondary outcome was colorectal cancer recurrence. We defined recurrence within a 4-yr window after surgery. As recommended by a panel of experts with SEER-Medicare data, colorectal cancer recurrence was defined as an ICD-9 metastasis code (197.5) or receipt of chemotherapy 16 months or more after the date of surgery and/or radiation therapy 12 months or more after the date of surgery.[36–37] Radiation therapy was identified using the ICD-9 codes 92.2, V58.0, V66.1, and V67.1 and CPT code 77xxx. MedPAR, National Claims History, and Standard Analytical File were evaluated for chemotherapy administration. The following ICD-9 codes were used to identify use of chemotherapy: chemotherapy administration (99.25), encounter for antineoplastic chemotherapy (V58.1), cancer chemotherapy follow-up (V67.2), convalescence and palliative care following chemotherapy (V66.2), outpatient or physician administration of chemotherapy (Q0083–Q0085), and chemotherapeutic agents (Healthcare Common Procedure Coding System codes J9000–J9999 or G0355–G0363). CPT codes 964xx and 965xx were also included. Revenue center codes for injected chemotherapy (0331), oral chemotherapy (0332), and intravenous chemotherapy (0335) were also used to identify chemotherapy use from physician-supplier claims. This approach has been validated for use of 5-fluorouracil for colon cancer using SEER-Medicare data in a previous study.[38]

Covariates. From the SEER file, we included patient-level demographic and clinical variables including age, gender, race, marital status, SEER site, year of diagnosis, anatomical site, stage of disease at diagnosis, and Medicare date of death. We also noted socioeconomic factors measured at the census tract level (urban/rural residence, median income, and percent of residents with at least a high school diploma). Cases with anatomical site codes for cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum were included. Blood transfusions were noted from the MedPAR blood pints furnished variable.

As recommended by the National Cancer Institute,‖ we identified comorbid conditions using ICD-9-CM codes from MedPAR, Outpatient, and physician-supplier claims to calculate a comorbidity index modified from the Deyo adaptation of the Charlson comorbidity index.[39] We adopted Klabunde's 30-day rule out algorithm to incorporate comorbid condition codes from outpatient files.[40]

Colectomy. We examined MedPAR for surgical procedure codes. The use of an ICD-9-CM diagnosis code of V64.4 in conjunction with procedure codes for colectomy 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 included in the analytic cohort. If a patient had a colectomy and the codes for laparoscopy were not present, then the patient was assumed to have had an open colectomy.

Complications. To account for differences in perioperative complications, we searched Medicare claims data from surgery date till 30 days after surgery. Complications included retrieval of retained foreign body (CPT-4 49085, ICD-9 54.92), management of postoperative shock/hemorrhage (ICD-9 39.98), management of abdominal infection (CPT-4 45020, 45562, 45563, 49020, 49021, 49040, 49041, 49060, 49061, 49080, 49081, 75989, ICD-9 54.0, 54.91, 54.19), repair of an organ injury/laceration (CPT-4 38100, 44602, 44603, 44604, 44605, ICD-9 41.5, 44.61, 46.71, 46.73, 46.75, 48.71, 50.61, 51.91, 69.41), reoperative laparotomy (CPT-4 49002, 49000, 49010, ICD-9 54.12, 54.11, 54.21), management of wound complication (CPT-4 10060, 10061, 10120, 10121, 10140, 10180, 12020, 13160, 97601, 97602, ICD-9 54.61, 86.22), management of fistula (CPT-4 44640, 44650, 44660, 44661, 45800, 45805, 45820, 45825, ICD-9 46.72, 46.74, 46.76),

‖ http://healthservices.cancer.gov/seermedicare/program/comorbidity.html. Accessed October 10, 2011.

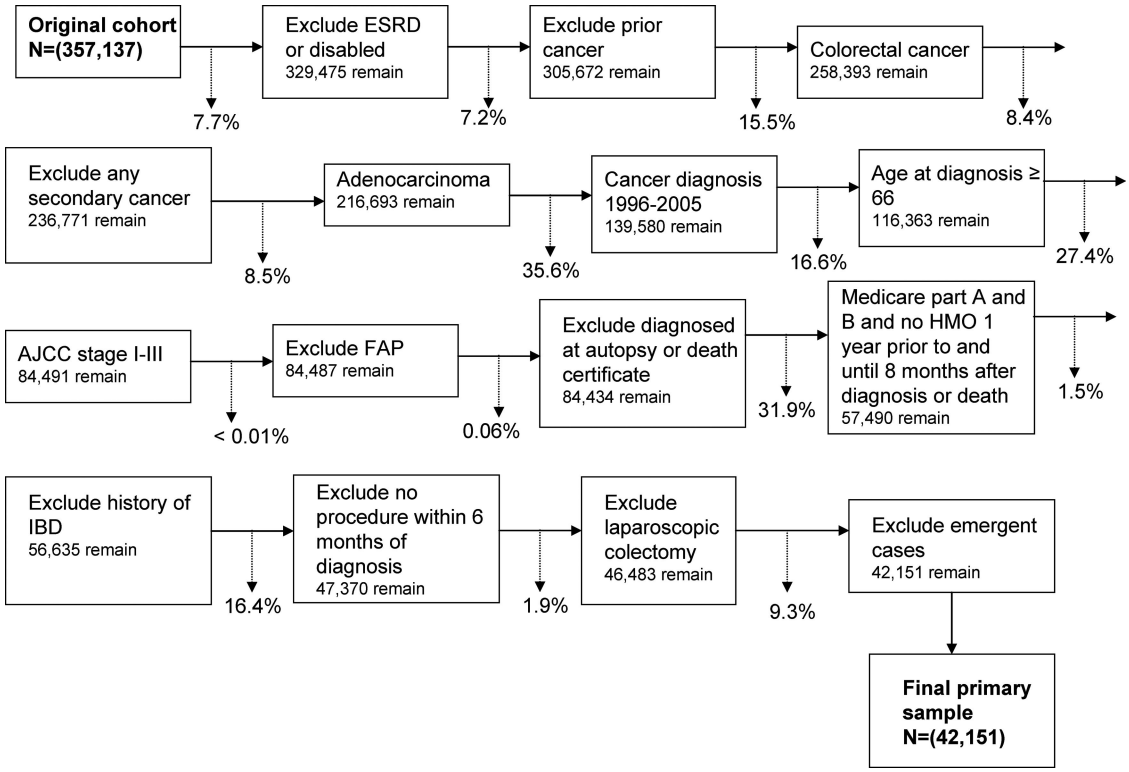

Fig. 1. Identification of analysis cohort. AJCC = American Joint Committee on Cancer; ESRD = end stage renal disease; FAP = familial adenomatous polyposis; HMO = health maintenance organization; IBD = inflammatory bowel disease.

management of bowel obstruction (CPT-4 44050), and management of stoma complication (CPT-4 44340, 44345, 44346, ICD-9 46.40, 46.41, 46.42, 46.43).[41]

Statistical Analysis

Patient characteristics were compared according to the presence or absence of epidural anesthesia and/or analgesia. For categorical variables, sample sizes with proportions were presented in each group. Pearson's chi-square test was used to compare the groups. For continuous variables, medians with interquartile ranges were presented. Wilcoxon rank sum test were used to compare the groups.

Survival time was defined from the date of surgery to all-cause mortality or last follow-up through December 31, 2009, indicated as censor. Kaplan–Meier survival curves were generated and the group comparison was based on the log-rank test. Based on the nature of the hospital clustered data, a marginal Cox model was constructed. This method uses the pseudolikelihood that yields a consistent estimate of covariate effects. A robust sandwich estimate was implemented in the model.[42] As a confirmatory analysis, using logistic regression, a propensity score was generated to predict the use of epidural anesthesia using the same covariates. The propensity score was then used as a continuous covariate to be included in the survival models.

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

All data were analyzed using SAS software version 9.2 (SAS Institute, Cary, NC) and R 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria). All comparisons used two-sided tests at a significance level of 0.05.

Results

Patient Selection

After applying the inclusion and exclusion criteria described above, we identified a primary cohort of 42,151 patients, of whom 22.9% (n = 9,670) had epidurals. The cohort for analysis of cancer recurrence comprised 40,377 patients, of whom 23.0% (n = 9,278) had epidurals at the time of resection. Figure 1 details the identification of the primary cohort. The median length of follow-up data was 5.0 yr (5.3 yr in the epidural group, 4.8 yr in the nonepidural group).

Patient Characteristics

There were a number of differences between the two groups in the primary analysis (table 1). Patients who received epidurals were slightly younger, had lower comorbidity scores, and were more likely to be males, white, married, and residing in Midwest SEER regions. Epidural use differed by American Joint Committee on Cancer stage as well, with stage I patients more likely to have an epidural. Those who received blood transfusion were less likely to have an epidural but the association was not significant (P = 0.16). When

analyzed by cancer location, epidural use was more common in distal tumors (rectosigmoid junction and rectum), but not other sites.

After controlling for hospitals, there was no significant association between epidural use and perioperative complications (conditional logistic regression odds ratio = 0.97, 95% CI[0.85, 1.1], $P = 0.60$).

Association Between Epidural Use and Overall Survival

5-yr overall survival was 61% in the epidural group and 56% in the traditional pain management group. Median survival in the epidural group was 7.24 yr (95% CI[6.96, 7.51]); in the nonepidural group, median survival was 6.09 yr (95% CI[5.97, 7.51]). Figure 2 shows Kaplan–Meier survival curves for the two groups; the curves were significantly different (log-rank test $P < 0.001$). 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 a significant association between epidural use and improved overall survival (adjusted hazard ratio = 0.91, 95% CI = [0.87, 0.94], $P < 0.001$). In the adjusted model, several covariates were significant predictors of mortality: older age, male gender, African-American race, unmarried state, higher comorbidity score, higher stage, poorly-differentiated tumors, distal location (descending colon through rectum), diagnosis before 2005, and blood transfusion were all associated with a higher hazard ratio for death. The association between blood transfusion and mortality was particularly strong (adjusted hazard ratio = 1.34, 95% CI [1.28, 1.40], $P < 0.001$). Residence in a census tract with a higher median income or higher percentage of people with high school diplomas was associated with a lower mortality hazard.

As a confirmatory analysis, we used the same covariates used in the adjusted Cox model (omitting blood transfusion and postoperative complication because they did not predict the use of epidural) to create a logistic regression model to predict a propensity score (likelihood of receiving an epidural). The c-statistic for the propensity score model was 0.647. We then incorporated this propensity score as a covariate in our 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 appreciably (hazard ratio = 0.92, 95% CI [0.88, 0.96], $P < 0.001$).

Association between Epidural Use and Colorectal Cancer Recurrence

Overall 4-yr cancer recurrence was 14.3% in the epidural group and 13.8% in the nonepidural group. In the unadjusted logistic regression, there was an association between epidural use and increased cancer recurrence (odds ratio = 1.14, 95% CI [1.05, 1.24], $P = 0.002$). Adjusting for demographic and clinical covariates, however, there was no significant difference in the odds of recurrence between the groups (odds ratio = 1.05, 95% CI [0.95, 1.15], $P = 0.28$). Of note, blood transfusion was a significant predictor of cancer recurrence in the adjusted model (odds ratio = 1.14, 95% CI = (1.03, 1.25), $P = 0.01$).

Discussion

Our results suggest an early and sustained beneficial effect of epidural use on all-cause mortality after colorectal cancer resection. These findings contrast those of the Multicenter Australian Study of Epidural Anaesthesia and Analgesia in Major Surgery (MASTER) trial,[43] a reanalysis of which also found no difference in mortality in the subset of patients undergoing surgery for abdominal malignancies.[26] Some literature, however, is consistent with our results. Christopherson *et al.* demonstrated improved survival up to 1.46 yr with epidural use in patients without metastases.[28] In addition, Gupta *et al.* found an association between epidural use and decreased all-cause mortality after resection of rectal (but not colon) cancers.[29] It is interesting to note that distal cancers were associated with a higher risk for mortality and recurrence than proximal in our analysis. Taken together with previous work, this suggests that there may be important clinical differences between rectal and more proximal cancers.

The 5-yr survival rates observed in this study (61% and 56% for epidural and nonepidural groups, respectively) are somewhat lower than others reported in the literature. For example, Gupta *et al.*[29] found 77.3% survival at a median follow-up of 2.7 yr, whereas Jayne *et al.*[44] reported a lower 67.8% overall survival at 3 yr. Both of these values, however, are higher than those seen in our analysis. This could be explained by differences in surgical technique, patient populations, or length of follow-up (our data provided longer term information).

Because immune surveillance is a primary determinant of cancer progression, it is logical to hypothesize that interventions aimed at reducing exposure to immunosuppressive factors would improve patient outcomes after potentially curative cancer resection. In colorectal cancer, however, this has been difficult to demonstrate. Our analysis found no association between epidural use and colorectal cancer recurrence. In that regard, our results fit well with the existing literature in colorectal cancer. 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 a relatively short follow-up period. In a subgroup analysis, however, they did demonstrate a lower risk of recurrence in older patients who received epidural analgesia.[25] Our logistic regression analysis indicates that increasing age is actually independently associated with a lower risk of cancer recurrence. Whether this is a true association or an effect of age on mortality hazard (and thus providing less time to observe for recurrence) remains to be seen. As mentioned previously, Myles *et al.*[26] evaluated

Table 1. Patient Characteristics by Type of Pain Management

Characteristics	Total Sample (n = 42,151)	Traditional Pain Management (n = 32,481)	Epidural Anesthesia and/or Analgesia (n = 9,670)	*P* Value
Age at diagnosis	—	—	—	—
Continuous age	77.8 (72.7, 83.2)	78.1 (72.8, 83.6)	77.1 (72.2, 82.1)	<0.001
Categorical age	—	—	—	<0.001
66–69	5,998 (14.2)	4,501 (13.9)	1,497 (15.5)	—
70–74	9,162 (21.7)	6,858 (21.1)	2,304 (23.8)	—
75–79	10,285 (24.4)	7,765 (23.9)	2,520 (26.1)	—
80–84	9,042 (21.5)	7,072 (21.8)	1,970 (20.4)	—
85+	7,664 (18.2)	6,285 (19.3)	1,379 (14.2)	—
Gender	—	—	—	<0.001
Female	24,223 (57.5)	18,352 (58.0)	5,371 (55.5)	—
Male	17,928 (42.5)	13,629 (42.0)	4,299 (44.5)	—
Race	—	—	—	<0.001
White	35,492 (84.2)	27,037 (83.2)	8,455 (87.4)	—
Black	2,744 (6.5)	2,239 (6.9)	505 (5.2)	—
Other	3,915 (9.3)	3,205 (9.9)	710 (7.3)	—
Marital status	—	—	—	<0.001
Married	20,928 (49.6)	15,813 (48.7)	5,115 (52.9)	—
Not married	19,712 (46.8)	15,514 (47.8)	4,198 (43.4)	—
Unknown	1,511 (3.6)	1,154 (3.5)	357 (3.7)	—
Education*	84.2 (75.0, 90.5)	84.0 (74.4, 90.4)	85.0 (77.4, 90.7)	<0.001
Income†	43,485 (32,850, 58,206)	43,445 (32,507, 58,757)	43,713 (34,026, 57,007)	0.17
Residence	—	—	—	0.02
Metropolitan	34,816 (82.6)	26,891 (82.8)	7,925 (81.9)	—
Urban	6,472 (15.4)	4,908 (15.1)	1,564 (16.2)	—
Rural	863 (2.0)	682 (2.1)	181 (1.9)	—
SEER region	—	—	—	<0.001
Midwest	9,266 (22.0)	5,826 (17.9)	3,440 (35.6)	—
Northeast	9,403 (22.3)	7,970 (24.6)	1,433 (14.8)	—
South	6,711 (15.9)	5,201 (16.0)	1,510 (15.6)	—
West	16,771 (39.8)	13,484 (41.5)	3,287 (34.0)	—
Charlson Index	—	—	—	<0.001
0	26,317 (62.4)	20,039 (61.7)	6,278 (64.9)	—
1	9,756 (23.2)	7,601 (23.4)	2,155 (22.3)	—
2	3,680 (8.7)	2,899 (8.9)	781 (8.1)	—
3+	2,398 (5.7)	1,942 (6.0)	456 (4.7)	—
Tumor differentiation	—	—	—	0.01
Well	3,565 (8.4)	2,802 (8.6)	763 (7.9)	—
Moderately	28,828 (68.4)	22,182 (68.3)	6,646 (68.7)	—
Poorly	7,830 (18.6)	6,058 (18.7)	1,772 (18.3)	—
Others/Unknown	1,928 (4.6)	1,439 (4.4)	489 (5.1)	—
AJCC stage	—	—	—	<0.001
I	11,506 (27.3)	8,757 (27.0)	2,749 (28.4)	—
II	16,697 (36.6)	13,021 (40.1)	3,676 (38.0)	—
III	13,948 (33.1)	10,703 (32.9)	3,245 (33.6)	—
Blood transfusion‡	—	—	—	0.16
No	38,218 (90.7)	29,415 (90.6)	8,803 (91.0)	—
Yes	3,933 (9.3)	3,066 (9.4)	867 (9.0)	—
Year of diagnosis	—	—	—	<0.001
1996	2,684 (6.4)	2,057 (6.3)	627 (6.5)	—
1997	2,638 (6.3)	1,974 (6.1)	664 (6.9)	—
1998	2,716 (6.4)	2,050 (6.3)	666 (6.9)	—
1999	2,608 (6.2)	1,919 (5.9)	689 (7.1)	—
2000	5,275 (12.5)	4,058 (12.5)	1,217 (12.6)	—
2001	5,259 (12.5)	3,990 (12.3)	1,269 (13.1)	—
2002	5,406 (12.8)	4,164 (12.8)	1,242 (12.8)	—
2003	5,475 (13.0)	4,291 (13.2)	1,184 (12.3)	—
2004	5,152 (12.2)	4,055 (12.5)	1,097 (11.3)	—
2005	4,938 (11.7)	3,923 (12.1)	1,015 (10.5)	—

(*continued*)

Table 1. Continued

Characteristics	Total Sample (n = 42,151)	Traditional Pain Management (n = 32,481)	Epidural Anesthesia and/or Analgesia (n = 9,670)	*P* Value
Cancer site	—	—	—	<0.001
Cecum	9,483 (22.5)	7,567 (23.3)	1,916 (19.8)	—
Ascending colon	7,510 (17.8)	5,952 (18.3)	1,558 (16.1)	—
Hepatic flexure	2,166 (5.1)	1,681 (5.2)	485 (5.0)	—
Transverse colon	3,130 (7.4)	2,447 (7.5)	683 (7.1)	—
Splenic flexure	1,059 (2.5)	837 (2.6)	222 (2.3)	—
Descending colon	1,579 (3.8)	1,239 (3.8)	340 (3.5)	—
Sigmoid colon	8,463 (20.1)	6,527 (20.1)	1,936 (20.0)	—
Rectosigmoid junction	3,350 (8.0)	2,447 (7.5)	903 (9.4)	—
Rectum	5,411 (12.8)	3,784 (11.7)	1,627 (16.8)	—

Continuous variables are presented as median (interquartile range) with *P* based on Wilcoxon rank-sum tests. Categorical variables are presented as counts (percent) with *P* based on Pearson chi-square tests.

* Education: Percent of individuals with at least a high school diploma at census tract level. † Income: Median household income at census tract level. ‡ Transfusion within 7 days after surgery.

AJCC = American Joint Committee on Cancer; SEER = Surveillance, Epidemiology, and End Results program.

the recurrence of many types of completely resected abdominal malignancies, of which 106 cases were colorectal, in groups randomized to either epidural or systemic analgesia. They found no significant difference in cancer recurrence between the groups (as a composite of the different malignancies), but the study had limited power to detect an effect on any particular malignancy. Taken together with these studies, our results suggest that the impact of epidural analgesia on colon cancer recurrence is minor at best.

The differences seen in analyses of colorectal cancer *versus* other malignancies highlight the difficulties facing investigators in this field. Differences in tumor biology (between and within cancer types), different surgical techniques, varying patient populations, challenges in defining recurrence, and difficulty with long-term follow-up all hamper firm conclusions. These are a few of the challenges that must be addressed in clinical trials. Given the long spans of time and large patient populations required, clinicians will have to wait quite a while for definitive results.

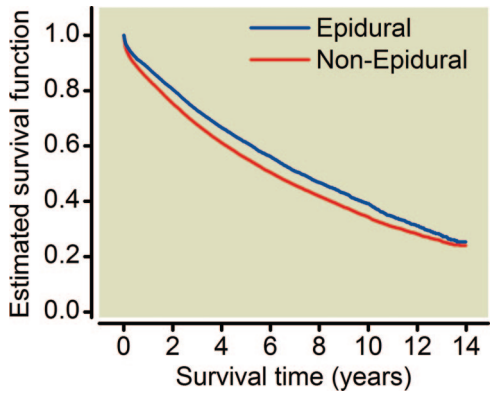

Fig. 2. Kaplan–Meier curves for overall survival. Log-rank test $P < 0.001$.

Of note, we found a significant association between perioperative blood transfusion and increased odds of cancer recurrence as well as an increased hazard for mortality. This is consistent with the increasingly recognized negative effects of allogeneic blood transfusion. In colon cancer patients, transfusion has previously been associated with increased odds of recurrence after surgery.[45] In a wider surgical population, Glance *et al.* found an association between blood transfusion and an increase in multiple perioperative complications, including an increased risk of death.[46] In our analysis, however, it is uncertain whether blood transfusion leads to worse outcomes or is simply a marker of a worse perioperative course or more aggressive tumor.

Table 2. Association between Epidural Use and All-cause Mortality

Models*	Hazard ratio	95% CI	*P* Value
Model 1A	0.86	(0.83, 0.89)	<0.001
Model 1B	0.91	(0.87, 0.94)	<0.001
Model 2A	0.92	(0.88, 0.96)	<0.001
Model 2B	0.92	(0.88, 0.96)	<0.001
Model 2C	0.92	(0.88, 0.96)	<0.001

Model 1A: epidural only (unadjusted). Model 1B: based on Model 1A, adjusted by age, gender, race, marital status, education, median income, year of diagnosis, Charlson score, tumor grade, cancer stage, blood transfusion, cancer site, and surgical complications. Model 2A: based on Model 1A, adjusted by propensity score†. Model 2B: based on Model 1A, adjusted by propensity score and blood transfusion. Model 2C: based on Model 2B, adjusted by propensity score and surgical complication.

* Models: Marginal clustered survival model using robust sandwich estimate. Hospitals where pain management was administered are clusters. † Age; gender; race; marital status; education; median income; year of diagnosis; Charlson score; tumor grade; cancer stage; cancer site; Surveillance, Epidemiology, and End Results program region; and residence type are the variables in the propensity score model to predict the likelihood of receiving an epidural.

This study has several strengths worth mentioning. The SEER-Medicare database is very large, provides detailed tumor information, and is centrally maintained by the National Cancer Institute. The data quality is very good and provides information from across the United States, not just a single center or region. To our knowledge, this is the first study in the anesthesiology literature to utilize this large database. The closest analysis to this field used the database to evaluate repeated exposure to anesthesia as one of many risk factors for non-Hodgkin's lymphoma.[47]

There are, however, important limitations to this analysis. It suffers from the same weaknesses inherent to all observational studies, namely susceptibility to bias, confounding, and effect-cause associations. It is possible that some of our results may be explained by unmeasured confounders or selection bias. We used propensity scores in an attempt to adjust for potential selection bias in treatment assignment, but we were limited to the covariates available in the database. It is important to remember that propensity scores only balance groups on known covariates, so unmeasured confounders may still remain. This limitation, combined with the modest discriminatory ability (c-statistic) of our propensity score model, suggests that successful balancing of covariates, although not assured, is likely.

Because much of the information on procedures comes from administrative claims, there are limited clinical data (surgical and anesthetic techniques, drugs administered, among others) on the care patients received. For example, we inferred a laparoscopic case converted to open if both codes for open procedures and laparoscopy were present. This could introduce bias, as these patients would be less likely to have epidurals and might have worse outcomes. The small proportion of these cases, however (less than 1%), would make any effects on the analysis quite small. In addition, because intraoperative use of an epidural is not billed separately (as opposed to placement solely for postoperative pain), the timing of epidural use (preoperative, intraoperative, or only postoperative) is unclear from this database. However, the combination of either a code for placement or the code for daily management is unlikely to miss a significant number of epidurals. Without any other means of identifying epidural use in this database, some level of misclassification will be inevitable. We contend, however, that misclassifying epidurals as controls would only dilute an association, not falsely indicate the presence of one.

One might argue that the study population should be patients who received preoperative epidural dosing to block the surgical stress response and/or in whom general anesthesia was avoided. In many of the previous studies discussed, general anesthesia was combined with regional analgesia. The main benefit proposed by those authors is reduction of anesthetic and opioid requirements. Certainly, many perioperative factors are immunosuppressive, but complete avoidance of general anesthesia and/or ablation of the surgical stress response, while desirable, are not always feasible and probably not necessary for a benefit under the hypotheses of this study. Even if patients did not receive epidural medications until the end of surgery, they would have required far less opioid analgesia (a potent immune suppressant) than nonepidural patients. Again, this would tend to bias toward a null result in our analysis.

Importantly, the database lacks a variable indicating cancer recurrence. Therefore, we were not able to assess disease-free survival and using chemotherapy, radiation therapy, and metastasis codes as proxies for recurrence may lead to cases of untreated recurrence going undetected, which could bias the result of the recurrence analysis. Also, because of 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). This may explain the early survival advantage in the epidural group, although we could not identify any differences in other perioperative complications. Finally, our dataset was limited to individuals ages 66 yr or older. However, patients in this age group have the highest incidence of colorectal cancer.[1]

In conclusion, this large population-based cohort study suggests that epidural anesthesia and/or analgesia is associated with improved survival in patients with nonmetastatic colorectal cancer undergoing resection. Our results do not support an association between epidural anesthesia and/or analgesia and recurrent disease. Prospective studies are needed to determine whether the association between epidural use and survival is causative.

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

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