Effect of epidural analgesia on long-term outcomes after curative surgery for pancreatic cancer: A single-center cohort study in Taiwan

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Abstract

Background: Whether epidural anesthesia and analgesia (EA) improves long-term outcomes after pancreatic cancer surgery remains controversial. We conducted this retrospective cohort study to investigate the influence of EA on cancer recurrence and overall survival after surgery for pancreatic cancer.

Methods: We conducted an electronic medical chart review of patients with pancreatic cancer who underwent curative resection at our hospital from 2008 to 2017 and were followed up until December 2019. Patient demographics, anesthetic and surgical characteristics, and pathologic features were also collected. The effects of EA on postoperative cancer recurrence and overall survival were evaluated using proportional hazards regression models with inverse probability of treatment weighting (IPTW) based on propensity scores to balance unequal distributions of observed covariates. For sensitivity analysis, multivariable regression modeling and quintile-stratified propensity adjustments were also used.

Results: Among the 252 included patients, the median follow-up period was 15.9 months (interquartile range 6.8–28.2 months), and 88 (35%) received EA after pancreatic cancer surgery. EA was not associated with greater cancer recurrence (IPTW adjusted HR: 0.98; 95% CI, 0.78%-1.24%; $p = 0.87$) or all-cause mortality (IPTW adjusted HR: 1.02; 95% CI, 0.82%-1.27%; $p = 0.85$) after pancreatic cancer resection. In sensitivity analysis, both the multivariable and stratified Cox regression analyses failed to demonstrate significant effects of EA on cancer recurrence and survival after surgery.

Conclusion: There were no significant associations between EA and cancer recurrence and overall survival after curative surgery for pancreatic cancer. Prospective studies should be considered to elucidate the relationship between EA and cancer outcomes after pancreatic cancer surgery.

Keywords: Cancer recurrence; Epidural analgesia; Inverse probability of treatment weighting; Overall survival; Pancreatic cancer

1. INTRODUCTION

Pancreatic cancer is the seventh leading cause of cancer-related mortality and fourth most common cancer worldwide.[1] In 2018, an estimated 400,000 patients were diagnosed with and died of pancreatic cancer around the world.[2] Despite advances in miscellaneous treatments, the 5-year survival rate remains as low as 9%, and 85% of the patients suffer from cancer recurrence after curative resection.[3] Although surgical resection is the main curative treatment for pancreatic cancer, it may induce the systemic dissemination of malignant cells and potentially trigger cancer recurrence.[4] Common risk factors for recurrence after surgical resection of pancreatic cancer include elevated serum CA-199 level, tumor size, lymph node involvement, absence of adjuvant therapy, and lack of an R0 resection margin.[5,6]

Immunological responses have been reported to potentially protect against tumor recurrence and metastasis, and Melamed et al demonstrated that natural killer cells may play an important role in resisting tumor metastasis.[7] Increasing evidence has shown that surgery and perioperative pain induce the production of stress hormones and suppress the immune system including lymphocyte function, cytokine expression, and antibody production, which is correlated with susceptibility to tumor cell retention and metastasis.[8,9] Moreover, systemic opioid administration causes the depression of both humoral and cellular immunity, which may favor cancer recurrence, and clinical evidence supports that avoiding opioid analgesics and general anesthesia, which is also known to suppress the immune system, may reduce the risk of cancer recurrence.[10,11] In particular, regional anesthesia alone or combined with general anesthesia has been shown to mediate pain stimuli in the perioperative period and has been suggested to lower the recurrence rate and prolong progression-free survival in several types of cancers, including breast, laryngeal, prostate, and colorectal cancer.[12–17] However, clinical studies evaluating the association between perioperative epidural anesthesia and analgesia (EA) and long-term

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oncological outcomes after primary pancreatic cancer surgery are lacking. Therefore, we conducted this retrospective cohort study to investigate this issue. We hypothesized that EA may reduce the risk of recurrence and mortality after curative surgery for pancreatic cancer. To more accurately evaluate the effects of EA on recurrence-free and overall survival after pancreatic cancer surgery, we used inverse probability treatment weighting (IPTW) based on propensity score to balance the distributions of observed variables and control for potential confounding effects.

2. METHODS

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH no. 2018-06-009CC). Patients who underwent surgical resection of pancreatic cancer between January 2008 and December 2017 at our hospital were retrospectively collected from the institutional electronic medical database. The following exclusion criteria were applied: secondary pancreatic cancer, a prior diagnosis of cancer, benign tumor, recurrent tumor, stage IV disease, palliative surgery, and missing demographic, and pathological data. The patients were further divided into two groups: patients who received general anesthesia combined with intra- and postoperative EA, and those given general anesthesia alone.

2.1. Analgesic Management

All patients in both groups underwent general anesthesia according to the following protocol: induction with fentanyl (1–3 μg/kg), propofol (1–2.5 mg/kg), and cisatracurium (1 mg/kg), and maintenance with inhalation agents including sevoflurane or desflurane. For the patients in the EA group, an epidural catheter was placed preoperatively between thoracic vertebra T9 to T11. A test dose with 20 mg of xylocaine was given through the epidural catheter to ensure the effectiveness. After the induction of anesthesia, 150 mg of xylocaine with 50 μg fentanyl was given as a loading dose, and 0.25% bupivacaine was continued at an infusion rate of between 5 and 10 mL/hour intraoperatively. EA was kept for 48–72 hours postoperatively as patient-controlled analgesia. After the epidural catheter was removed, the analgesics were generally shifted to nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. For those without EA, intravenous morphine was used for primary pain control after surgery.

2.2. Clinicopathologic Characteristics

We collected baseline characteristics and potentially prognostic factors of pancreatic cancer from the electronic medical records, including age, gender, American Society of Anesthesiologists (ASA) physical status classification, comorbidities, preoperative hemoglobin, platelet count, prothrombin time, activated partial thromboplastin time, bilirubin, albumin, anesthesia time, type of surgery, laparoscopic-assisted surgery, pathological features (tumor size and differentiation, lack of an R0 resection, lymphovascular or perineural invasion), tumor staging, and perioperative blood transfusion. To quantify the severity of comorbidities we used the Charlson comorbidity index (CCI), which results in a single comorbidity score from the sum of weighted categories of different comorbidities (diabetes mellitus, chronic kidney disease, congestive heart failure, and so on). A higher score indicates a higher likelihood of morbidity and mortality.

2.3. Follow-up and Outcomes

All patients were closely followed up after surgery at our outpatient department, with a lost to follow-up rate of only 4.1%. Abdominal computed tomography was performed every 3 months in the first 2 years and then annually thereafter. The radiologists and surgeons determined the presence of cancer recurrence mainly based on imaging studies (computed tomography, magnetic resonance imaging, and whole body bone scan). We recorded the dates of confirmed recurrence and expiration, and set the primary endpoint as recurrence-free survival, defined as the time from the date of surgery to the date of cancer recurrence. The secondary endpoint was overall survival, which was defined as the time from the date of surgery to the date of death. For patients without an event of cancer recurrence or death, their survival times were recorded as the corresponding censored observations.

2.4. Statistical Analysis

Comparisons of baseline attributes between the epidural and nonepidural groups were performed using the chi-square test for categorical covariates and either t tests or Wilcoxon rank-sum test for continuous covariates, as appropriate. The Kaplan-Meier method was applied to compare the recurrence-free survival and overall survival curves between groups. Univariate Cox regression analysis was used to assess the effect of covariates on recurrence-free or overall survival. Significant variables associated with recurrence-free or overall survival in univariate analysis were considered to be candidates for stepwise model selection procedures in multivariable models. Associations between EA and outcomes were further examined after adjusting for the determined predictors of the multivariable models.

Given the potential imbalance of measured confounders between the two groups, propensity scores based on a list of patient characteristics were generated to estimate the probability of receiving an epidural (Supplementary Table 1, http://links.lww.com/JCMA/A106). An IPTW method based on propensity score was used to eliminate possible confounding effects from the imbalances in collected variables. The inverse of estimated probability was then used for further weighted regression analysis, and 1% of cases at the end of weighting distribution were truncated to diminish the impact of large weights on the analytical results. Weighted Cox regression analysis was used to examine the associations between EA and cancer recurrence or overall survival based on IPTW. For sensitivity analysis, all subjects were divided into five groups of equal size using the quintiles of the estimated propensity scores. Stratified Cox regression analysis was performed to obtain a pooled hazard ratio (HR) across the five strata. The significance level for all hypotheses was 0.05 for a two-tailed test. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

3. RESULTS

A total of 252 patients were included in the analysis, of whom 88 (34.9%) received EA during surgery and for postoperative pain control. The median follow-up period for all patients was 15.9 months (interquartile range: 6.8–28.2 months). There was no significant difference in postoperative pain score between the two groups, and the mean daily pain scores in the numeric rating scale ranged between 2.2 and 3.6 during the first 5 postoperative days. Before IPTW, the patients in the EA group tended to have greater blood loss during surgery and less laparoscopic surgery, and most patients received EA before 2014 (Table 1). However, after IPTW adjustment, most of the collected variables were balanced between the EA and non-EA groups (Table 1).

3.1. Epidural Analgesia and Recurrence Risk

In the univariate analysis, EA was not associated with cancer recurrence (HR = 1.12, p = 0.49, Fig. 1A) after curative surgery for pancreatic cancer. Multivariable analysis after model selection identified three independent predictors of cancer recurrence:

Table 1

Patient demographics

	Before IPTW			After IPTW		
	EA group (n = 88)	Non-EA group (n = 164)	Standardized difference	EA group (n = 232)	Non-EA group (n = 253)	Standardized difference
Sex, male	51 (58.0 %)	84 (51.2 %)	13.6	130 (56.1%)	137 (54.1%)	4.1
Age older than 70 years	33 (37.5 %)	71 (43.3 %)	11.8	117 (50.4%)	104 (41.1%)	18.7
Charlson comorbidity index	5 ± 2	5 ± 2	20.9	5 ± 2	5 ± 2	9.9
Hemoglobin, g•dL^{-1}	12.1 ± 1.7	12.1 ± 1.6	3.3	11.8 ± 1.7	12.0 ± 1.6	13.2
International normalized ratio	1.02 ± 0.06	1.04 ± 0.09	22.3	1.02 ± 0.06	1.04 ± 0.09	19.8
Platelet count, 1000 mL^{-1}	249 ± 104	238 ± 84	11.8	244 ± 107	235 ± 83	9.4
Albumin, g•dL^{-1}	3.77 ± 0.51	3.73 ± 0.53	8.2	3.68 ± 0.51	3.73 ± 0.54	9.8
Total bilirubin, mg•dL^{-1}*	0.88 ±1.63	0.57 ± 1.55	19.5	0.80 ± 1.49	0.67 ± 1.62	8.7
CA19-9, U/mL*	7.29 ± 3.00	7.56 ± 3.48	8.4	7.87 ± 2.92	7.59 ± 3.34	8.9
Anesthesia time, min*	9.15 ± 0.42	9.15 ± 0.59	1.4	9.12 ± 0.43	9.14 ± 0.55	4.5
Blood loss, mL*	9.09 ± 1.20	8.41 ± 1.71	46.0	8.75 ± 1.45	8.63 ± 1.65	7.4
Blood transfusion	54 (61.4 %)	90 (54.9 %)	13.2	146 (62.8%)	145 (57.3%)	11.1
Laparoscopic or robotic surgery	8 (9.1 %)	64 (39.0 %)	74.8	44 (19.1%)	71 (28.0%)	21.2
Tumor size larger than 5 cm	30 (34.1 %)	47 (28.7 %)	11.7	85 (36.5%)	79 (31.4%)	10.8
Lymphovascular invasion	54 (63.5 %)	111 (68.5 %)	10.5	138 (60.6%)	166 (66.3%)	11.9
Perineural invasion	64 (79.0 %)	139 (85.8 %)	17.9	172 (78.2%)	204 (81.6%)	8.3
Lack of an R0 resection	10 (11.6 %)	34 (20.9 %)	25.2	36 (16.0%)	45 (17.8%)	4.9
Lymph node involvement	46 (52.3 %)	88 (53.7 %)	2.8	102 (43.8%)	132 (52.2%)	16.9
Year of surgery			117.5			7.9
Before 2014	73 (83.0 %)	54 (32.9 %)		126 (54.5%)	128 (50.5%)	
In or after 2014	15 (17.0 %)	110 (67.1 %)		106 (45.5%)	125 (49.5%)	

*On base-2 logarithmic scale. Values are presented as mean ± SD, counts (percent), or median (interquartile range). Standardized difference is the difference in mean, proportion or rank divided by the pooled standard error, expressed as percentage; imbalance was defined as an absolute value greater than 20 (small effect size).
CA19-9 = carbohydrate antigen 19-9; IPTW = inverse probability of treatment weighting.

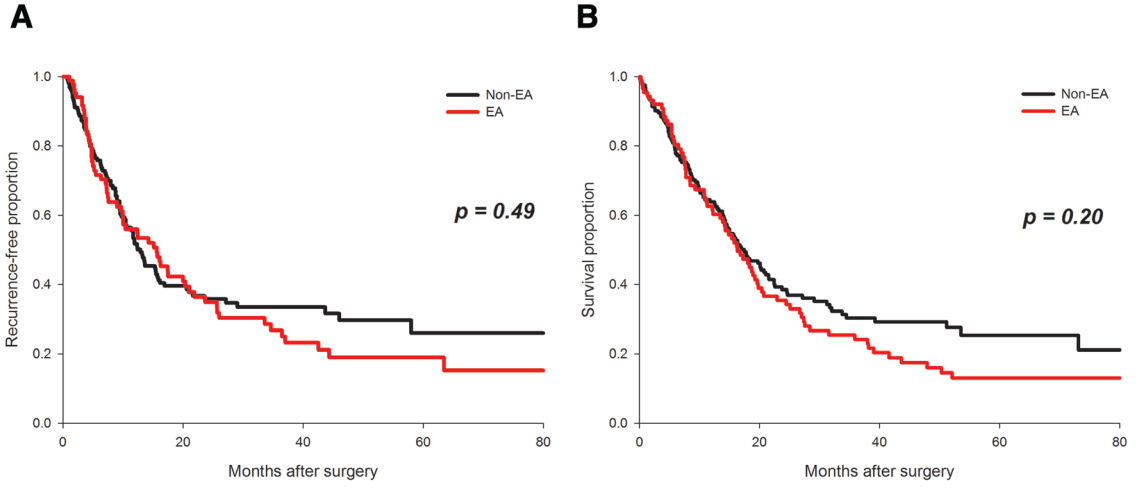

Fig. 1 Kaplan-Meier curves for cancer recurrence and all-cause mortality in the EA and non-EA groups. No significant differences in cancer recurrence (A) or all-cause mortality (B) after pancreatic cancer resection were found between the EA and non-EA groups. EA = epidural anesthesia and analgesia.

hemoglobin level (HR = 0.83), CA19-9 level (on base-2 logarithmic scale, HR = 1.07), and pathologic lymphovascular invasion (HR = 1.99) (Table 2). The effect of EA on cancer recurrence remained non-significant after adjustments for these risk factors (HR = 1.11, 95% CI, 0.80%-1.54%, p = 0.52). After IPTW adjustment, weighted Cox regression analysis showed a nonsignificant difference in the risk of cancer recurrence between the two groups (HR = 0.98, 95% CI, 0.78%-1.24%, p = 0.87). The sensitivity analysis also showed no significant effect of EA on cancer recurrence in the quintile-stratified analysis (HR = 1.11, 95% CI, 0.76%-1.63%; p = 0.59).

3.2. Epidural Analgesia and the Risk of Mortality

In the univariate analysis, a borderline significant association was noted between EA and the risk of mortality after curative surgery for pancreatic cancer (HR = 1.21, p = 0.20, Fig. 1B). The multivariable model identified five independent risk factors of all-cause mortality: low albumin level (HR = 0.62), CA19-9 level (on base-2 logarithmic scale, HR = 1.11), intraoperative blood loss (on base-2 logarithmic scale, HR = 1.24), pathologic perineural invasion (HR = 1.65), and the lack of an R0 resection (HR = 1.49) (Table 3). The effect of EA on all-cause mortality remained non-significant after adjustments for these significant

Table 2

Forward model selection for recurrence-free survival before weighting

	HR	95% CI	*p*
Epidural analgesia	1.11	0.80-1.54	0.522
Hemoglobin	0.83	0.75-0.91	<0.001
CA19-9*	1.07	1.02-1.13	0.006
Lymphovascular invasion	1.99	1.38-2.88	<0.001

*On base-2 logarithmic scale. Hemoglobin and CA19-9 were treated as continuous variables in the analysis.

CI = confidence intervals; HR = hazard ratio; CA19-9 = carbohydrate antigen 19-9.

predictors (HR = 1.06, 95% CI, 0.78%-1.44%, p = 0.72), similar to the results of weighted Cox regression analysis (HR = 1.02, 95% CI, 0.82%-1.27%, p = 0.85) based on IPTW adjustment. The sensitivity analysis also showed no significant effect of EA on all-cause mortality in the quintile-stratified analysis (HR = 1.17, 95% CI, 0.83%-1.65%, p = 0.37).

4. DISCUSSION

This study is the first to investigate the effects of EA on long-term outcomes of pancreatic cancer after curative resection. Our results demonstrated that EA was not significantly associated with recurrence-free or overall survival after pancreatic cancer surgery. In this study, we took major prognostic factors into consideration and used IPTW to minimize imbalances in the collected variables between the EA and non-EA groups and eliminate possible confounding effects. Moreover, we used multivariable models and other propensity score-based methods for sensitivity analysis to ensure consistency of the estimated results. From a methodological perspective, we used novel and sound analytical approaches to examine a hypothetical relationship between EA and cancer recurrence or overall survival after pancreatic cancer surgery, and our results provide new evidence to challenge the hypothetical benefit of EA on long-term oncological outcomes.

An increasing number of studies support our results by showing that regional anesthesia has no benefit on improving postoperative oncological outcomes. For example, Wu et al conducted a retrospective study and demonstrated that thoracic EA had a nonsignificant effect on recurrence or survival after resection of nonsmall cell lung cancer.[18] In addition, Juraj et al investigated the oncological outcomes of patients receiving prostatectomy with epidural anesthesia compared with general anesthesia with systemic opioids.[19] In contrast to other studies,[20,21] they found that the patients who received general anesthesia were not at an increased risk of cancer recurrence or cancer-related mortality. In addition, a meta-analysis of 10 studies and 3254 patients evaluated the postoperative prognosis of cancer in patients under general anesthesia and combined epidural-general anesthesia,[22] and the final results revealed no significant differences between the two groups in postoperative cancer recurrence or metastasis rate in patients with breast cancer, prostate cancer, colorectal cancer, and gastroesophageal cancer.

Table 3

Forward model selection for overall survival before weighting

	HR	95% CI	*p*
Epidural analgesia	1.06	0.78-1.44	0.715
Albumin	0.62	0.45-0.84	0.002
CA19-9*	1.11	1.06-1.16	<0.001
Blood loss*	1.24	1.11-1.38	<0.001
Perineural invasion	1.65	1.05-2.59	0.030
Lack of an R0 resection	1.49	1.03-2.14	0.033

*On base-2 logarithmic scale. CA19-9 and blood loss were treated as continuous variables in the analysis.

CI = confidence intervals; HR = hazard ratio; CA19-9 = carbohydrate antigen 19-9.

Few studies have focused on the associations between EA and oncological outcomes after pancreatic cancer surgery. Tyler et al conducted a retrospective analysis to assess the effects of perioperative management on survival in patients undergoing curative resection of pancreatic adenocarcinoma.[23] They suggested that using perioperative EA could improve survival but not reduce perioperative opioid administration, which did not support the opioid-associated immunosuppression effect that leads to cancer recurrence. However, a relatively small cohort (144 patients) was investigated in their study, and some major prognostic factors were not included in the analysis. As a result, potential confounding effects and selection bias may have caused problems in the interpretation of their research findings.

Mechanisms supporting the hypothesis that regional anesthesia may reduce cancer recurrence and metastasis after curative surgeries include a reduction in the administration of opioids and general anesthesia, attenuation of surgical stress, anti-inflammation effect of local anesthetics and thereby inhibition of postoperative immunosuppression. However, both epidurally and intravenously administered fentanyl have been reported to achieve similar serum fentanyl concentrations at an equianalgesic dosage.[24] Accordingly, perioperative EA does not appear to reduce serum opioid concentration compared to general anesthesia alone, and therefore cannot avoid an immunosuppression effect.[23] Nevertheless, pancreatic cancer surgery is suitable for evaluating the influence of EA on oncological outcomes due to its high cancer recurrence and low survival rates after tumor resection, and the course of pancreatic cancer tends to be fully observed compared with other types of cancer.

Our results also indicated that the risk factors for diminished overall and recurrence-free survival from pancreatic cancer were perineural invasion, lymphovascular invasion, operative blood loss, longer anesthesia time, lack of R0 resection, increased preoperative serum CA-199 level, and lower preoperative serum albumin and hemoglobin levels, most of which are consistent with prognostic factors proposed in previous studies.[25] In contrast to the patients with postoperative cancer recurrence, those without recurrence had lower operative blood loss (geometric means 458 mL and 328 mL, respectively), and the difference was statistically significant. Hiroshi et al also reported that increased intraoperative blood loss in patients undergoing curative resection of stage II/III pancreatic cancer was an independent risk factor for overall and recurrence-free survival in a retrospective study.[26] Operative blood loss in curative surgeries for other digestive carcinomas including hepatocellular carcinoma, gastric cancer and colorectal cancer has also been correlated with cancer recurrence.[27–31] Increased operative blood loss is closely related to allogeneic blood transfusion, which may cause tumor cell spreading due to downregulation of the immune response.[32,33] Kamei et al also found that intraoperative blood loss in colorectal cancer resection was an independent risk factor for peritoneal recurrence, and the correlation was statistically significant even in patients without blood transfusion.[29] This indicates that increased intraoperative blood transfusion is not the only cause of cancer recurrence. Enhanced surgical stress caused by operative blood loss may also result in decreased survival from pancreatic cancer.[34–36]

There are several limitations to our analysis. First, as with other retrospective studies, selection bias and unmeasured confounders were possible since the patients were not randomly assigned to receive EA or not in this study. Although IPTW was used to cancel out potential selection bias in treatment assignment, only observed covariates could be balanced through the process. Second, this study was conducted at a single center with

similar epidural regimens and anesthetic management. Different races, distributions of patient attributes or treatment protocols may have led to different results. Third, we did not evaluate the impact of perioperative opioid consumption due to the unavailability of related data in the electronic medical records.

In conclusion, this retrospective cohort study demonstrated that EA was not significantly associated with improved survival or lower recurrence rate in patients undergoing curative resection of pancreatic cancer. Our results provide valuable information about the risk of cancer progression after pancreatic cancer surgery, and further prospective investigations are encouraged to further elucidate the complex relationships between EA and postoperative cancer outcomes.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A106.

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