J Chin Med Assoc

ORIGINAL ARTICLE

Does epidural analgesia improve the cancer outcome in hepatocellular carcinoma after resection surgery? A retrospective analysis

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Abstract

Background: Few studies have investigated the association between epidural analgesia (EA) and oncologic outcomes in patients following hepatocellular carcinoma (HCC) resection.

Methods: This retrospective study was conducted at a single medical center using electronic medical records. Patients with non-metastatic primary HCC undergoing tumor resection between January 2005 and December 2011 were classified into two groups based on their use of EA or intravenous analgesia. Multivariate Cox regression analyses were used to evaluate the associations between EA and recurrence-free (RFS) and overall (OS) survival. The patients were also propensity score-matched by demographic and important clinicopathologic variables.

Results: A total of 744 patients (58.5% receiving EA) with a median follow-up time of 64.5 months and 277 matched pairs were included in the analyses before and after matching. No significant association between EA and cancer recurrence or overall mortality was found before matching (RFS: adjusted hazard ratio [HR] = 0.97, 95% CI: 0.80-1.17; OS: adjusted HR = 0.95, 95% CI: 0.71-1.26). After matching, the association between EA and cancer recurrence or overall mortality remained nonsignificant (RFS: HR = 0.89, 95% CI: 0.68-1.17; OS: HR = 1.20, 95% CI: 0.81-1.78).

Conclusion: This study did not support a definite association between EA and cancer recurrence or OS in patients with primary HCC after surgical resection.

Keywords: Cancer; Epidural anesthesia; Hepatocellular carcinoma; Recurrence

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is a lethal disease with a poor prognosis and higher incidence in eastern Asia and Africa.[1] HCC poses a significant economic burden on healthcare systems in these countries. Surgical removal of the primary tumor remains the mainstay of treatment for HCC.[2] However, postoperative recurrence plays an important role in determining the patients' survival. The suppression of host immunity during the perioperative period can have a potentially deleterious effect on long-term clinical outcomes.[3] Surgical manipulations may release tumor cells into the blood stream and lymphatic system, which promotes local recurrence and metastasis.[4] General anesthesia has also been postulated to be linked to tumor recurrence due to its effect on immunosuppression. In animal models, opioids have been shown to suppress cellular and humoral immune function and also stimulate angiogenesis, which may promote tumor progression.[5] Nonopioid analgesia has been reported to be beneficial in preserving the function of natural killer cells and diminishing cancer cell dissemination in animals.[6]

Regional anesthetic techniques can effectively attenuate a surgical stress response by blocking noxious afferent input transmitted to the central nervous system, reducing the consumption of opioids, and preserving host immunity.[7] Patients with breast and prostate cancer receiving regional analgesia have been reported to have a lower risk of cancer recurrence compared with those receiving intravenous opioid analgesia.[8,9] Opioids given intrathecally in small amounts provide great pain relief postoperatively, while further retaining host defense mechanisms and avoiding large intravenous doses of opioids.[10]

Perioperative epidural analgesia (EA) has been reported to prolong postoperative long-term survival in miscellaneous cancers, including prostate cancer, colorectal cancer, and breast cancer.[11] However, few studies have investigated the association between EA and oncologic outcomes in patients with HCC. One retrospective study reported that treatment of small HCC with percutaneous radiofrequency ablation under general anesthesia resulted in a lower risk of cancer recurrence compared to EA.[12] However, the study was limited by a small number of patients, and the interpretation of its results may have been limited by inadequate statistical power. In addition, it is difficult to extrapolate the results from the setting of percutaneous radiofrequency ablation for small HCC to resection surgery for large HCC. Accordingly, we conducted this retrospective cohort study to investigate the effect of EA on long-term cancer outcomes in patients after HCC resection surgery. Specifically, we tested the hypothesis that EA may be associated with improved recurrence-free survival (RFS) and overall survival (OS) in patients with nonmetastatic HCC after surgical resection of the primary tumor.

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2019) 82: 295-299.

Received August 28, 2018; accepted November 5, 2018.

doi: 10.1097/JCMA.0000000000000054.

2. METHODS

Ethics approval was granted by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (IRB-TPEVGH No. 2015-11-010CC). The need for written informed consent was waived, as all study materials were anonymized and deidentified before processing. We reviewed the electronic medical records of all patients undergoing liver resection at our medical center from January 2005 to December 2011. Patients with reoperation, liver transplantation, or missing critical data about baseline attributes or analgesic techniques were excluded. Based on the pathology reports, surgeries for benign lesions, metastatic tumors, non-HCC primary intrahepatic cancer, or recurrent HCC were also excluded. In addition, primary HCCs with lymph node involvement or distant metastasis diagnosed at the time of surgery were also excluded. Finally, patients with a preoperative platelet count <100 000 cells·μL^{-1} or international normalized ratio (INR) >1.3 were excluded. The remaining patients were included into the study and further classified into two groups based on their perioperative use of EA or intravenous analgesia (Fig. 1).

2.1. Analgesic management

At our center, EA is commonly given to patients undergoing major abdominal surgeries. Patients scheduled to receive EA for perioperative pain control typically had epidural catheters implanted at the lower thoracic spine, 1 day before surgery. The function of the epidurals was tested with one bolus of lidocaine 2% promptly after catheter placement. EA was administered intraoperatively for anesthesia and postoperatively for analgesia. A loading dose of lidocaine 60 to 100 mg was given before surgical incisions, followed by a continuous infusion of bupivacaine 0.25% or 0.5% at a rate of 5 to 10 mL·h^{-1}. EA was further typically used for 48 to 72 hours after surgery. However, a sizable portion of patients undergoing abdominal surgery did not have epidurals due to existing contraindications (eg, coagulopathy due to hepatic diseases) or the preference of the surgeons or patients. Typically, the patients with a preoperative platelet count <100 000 cells·μL^{-1} or INR >1.3 were considered to be inappropriate for epidural catheter implantation. Other contraindications to EA included induced coagulopathy by antiplatelet or anticoagulant drugs, critical aortic stenosis, sepsis, or physical frailty. Those without epidurals or with failed epidurals were given intravenous patient-controlled or on-demand opioid analgesia as an alternative. Intravenous patient-controlled analgesia was administered by an ambulatory infusion pump (Gemstar Yellow, Hospira, IL, USA) to deliver morphine with infusion rates of 0.5 to 1.0 mg·h^{-1} and boluses of 1 mg with a lockout time of 6 minutes.

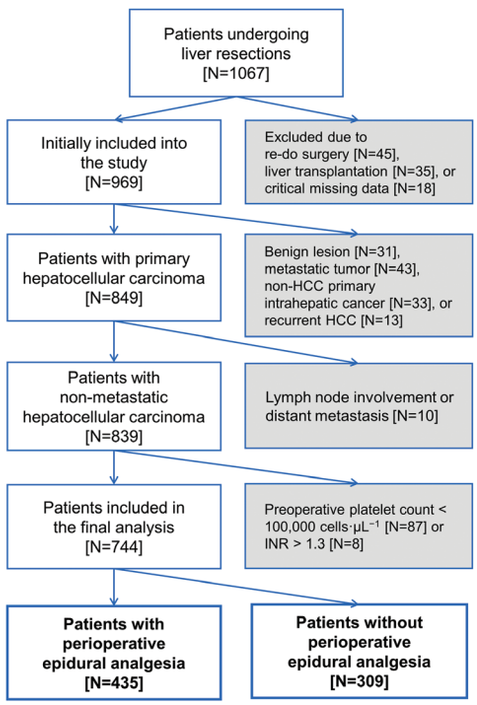

Fig. 1 Flow diagram for patient selection.

2.2. Data collection

One specialist anesthesiologist reviewed the electronic medical records of the included patients and collected relevant clinicopathologic variables. The covariates included age, sex, American Society of Anesthesiologists (ASA) class, hepatitis profile, liver cirrhosis, preoperative platelet count and INR, baseline concentrations of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alpha-fetoprotein, diameter and number of tumors, microvascular invasion, extracapsular invasion, and anesthesia time.[13,14] The primary outcome was RFS, defined as the time from the date of surgery to the date of first tumor recurrence. Recurrence was determined by the presence of locoregional or metastatic deposits in imaging studies (eg, ultrasonography, computerized tomography, and magnetic resonance imaging). The secondary outcome was OS, defined as the time from the date of surgery to the date of death. The records of outpatient clinic visits and admissions were used to determine each patient's current status. The patients were followed up until the end of September 2018. For those without cancer recurrence or death, the survival times were defined as the corresponding censored observations.

2.3. Statistical analysis

Patient characteristics were compared between the EA and non-EA groups using the χ^2 for categorical variables and either the *t* test or Wilcoxon rank sum test for continuous variables, as appropriate. The Kaplan–Meier method was used to depict the RFS and OS curves of the two groups, and the log rank test was used to compare survival distributions between them. Univariate Cox regression analysis was used to evaluate the effects of variables collected in the study on RFS or OS. Significant predictors of RFS or OS in the univariate analysis were incorporated in the multivariate regression model to evaluate the adjusted effects of EA. In addition, the patients in the EA and non-EA groups were further matched using propensity scores generated by logistic regression analysis (Supplementary Table) to ensure sufficient balance in the collected demographic and clinicopathologic variables. Stratified Cox regression analysis with matched pairs was used to assess the effects of EA on cancer recurrence and mortality after matching. $p < 0.05$ was considered to be statistically significant. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) was used for all analyses.

3. RESULTS

A total of 744 patients with a median follow-up time of 64.5 months were analyzed in this study, of whom 435 received EA (58.5%). Comparisons of patient characteristics between the EA and non-EA groups before and after propensity score matching are presented in Table 1. A significant difference was only noted in abnormal total bilirubin level between the two groups ($p = 0.007$). After matching, 277 matched pairs were included for further analysis, and no significant differences were found in patient characteristics between the EA and non-EA groups.

3.1. The association between EA and cancer recurrence

The 5-year RFS rates of HCC were 36.6% (95% CI: 31.7%-41.5%) and 36.7% (95% CI: 31%-42.4%) in the EA and non-EA groups, respectively. There was no significant difference in RFS after surgery between the two groups ($p = 0.81$ by the log rank test, Fig. 2). Univariate analysis identified several significant

Table 1

Characteristics of patients receiving epidurals or not before and after matching

	Before matching			After matching		
	EA group (N = 435)	Non-EA group (N = 309)	Standardized difference	EA group (N = 277)	Non-EA group (N = 277)	Standardized difference
Age, y	60 ± 14	61 ± 12	5.3	61 ± 14	61 ± 12	0.1
Sex, male	349 (80.2%)	238 (77.0%)	7.8	217 (78.3%)	219 (79.1%)	1.8
ASA class ≥ 3	108 (24.8%)	73 (23.6%)	2.8	73 (26.4%)	68 (24.5%)	4.1
HBsAg positive	301 (69.2%)	209 (67.6%)	3.4	191 (69.0%)	188 (67.9%)	2.3
Anti-HCV Ab positive	86 (19.8%)	69 (22.3%)	6.3	62 (22.4%)	61 (22.0%)	0.9
Alcoholism	25 (5.7%)	13 (4.2%)	7.1	11 (4.0%)	13 (4.7%)	3.6
Liver cirrhosis	161 (37.0%)	122 (39.5%)	5.1	111 (40.1%)	110 (39.7%)	0.7
Platelet count, $10^3 \cdot \mu L^{-1}$	199 ± 74	192 ± 85	9.3	196 ± 73	193 ± 88	3.1
INR	1.02 ± 0.07	1.03 ± 0.07	13.8	1.03 ± 0.07	1.02 ± 0.07	1.3
Total bilirubin ≥ 1.0 $mg \cdot dL^{-1}$	91 (21.0%)	41 (13.3%)	20.4	46 (16.6%)	39 (14.1%)	7.0
AST > 40 IU/L	204 (47.0%)	152 (49.2%)	4.4	144 (52.0%)	138 (49.8%)	4.3
ALT > 40 IU/L	214 (49.2%)	174 (56.3%)	14.3	148 (53.4%)	153 (55.2%)	3.6
Alpha-fetoprotein > 20 $ng \cdot mL^{-1}$	221 (52.4%)	158 (54.5%)	4.2	149 (53.8%)	153 (55.2%)	2.9
Tumor diameter > 5 cm	176 (40.5%)	113 (36.6%)	8.0	108 (39.0%)	102 (36.8%)	4.5
Multiple nodules	84 (19.3%)	82 (26.5%)	17.3	65 (23.5%)	67 (24.2%)	1.7
Microvascular invasion	283 (65.1%)	203 (65.7%)	1.3	185 (66.8%)	184 (66.4%)	0.8
Extracapsular invasion	249 (57.2%)	170 (55.0%)	4.5	155 (56.0%)	150 (54.2%)	3.6
Anesthesia time, min*	8.49 ± 0.42	8.44 ± 0.43	13.1	8.46 ± 0.41	8.45 ± 0.44	3.3

Values were mean ± SD or counts (percent). Standardized difference is the difference in mean or proportion divided by the pooled standard error, expressed as percentage; imbalance is defined as absolute value > 20 (small effect size).

ALT = alanine aminotransferase; Anti-HCV Ab = hepatitis C antibody; ASA = American Society of Anesthesiologists; AST = aspartate aminotransferase; EA = epidural analgesia; HBsAg = hepatitis B surface antigen; INR = international normalized ratio.

*On base-2 logarithmic scale.

predictors of cancer recurrence, including hepatitis B surface antigen (HBsAg) positive, liver cirrhosis, higher levels of INR, AST, ALT and alpha-fetoprotein, larger tumor diameter, multiple nodules, microvascular invasion, extracapsular invasion, and longer anesthesia time. However, EA was not associated with the risk of postoperative cancer recurrence in the univariate analysis (hazard ratio [HR] = 1.02, p = 0.81) (Table 2). After adjusting for these significant covariates, the adjusted effect of EA on cancer recurrence was not significant in the multivariate model (HR = 0.97, 95% CI: 0.80-1.17, Table 3). In addition, the effect of EA on cancer recurrence in the stratified Cox regression analysis after matching remained nonsignificant (HR = 0.89, 95% CI: 0.68-1.17, p = 0.41).

3.2. The association between EA and OS

The 5-year OS rates were 74.8% (95% CI: 70.3%-79.3%) and 76.6% (95% CI: 71.3%-81.9%) in the EA and non-EA groups, respectively. No significant difference in long-term mortality after surgery was found between the two groups (Fig. 2, p = 0.68 by the log rank test). Univariate analysis revealed a number of significant risk factors for mortality, including older age, ASA class ≥ 3, liver cirrhosis, higher levels of AST and alpha-fetoprotein, larger tumor diameter, multiple nodules, microvascular invasion, extracapsular invasion, and longer anesthesia time. EA was not associated with the risk of long-term mortality in the univariate analysis (HR =1.06, p = 0.682) (Table 2). Similarly, the effect of EA on OS remained nonsignificant after adjusting for the aforementioned significant predictors (HR = 0.95, 95% CI: 0.71-1.26, Table 3). After matching, stratified Cox regression analysis also showed no significant effect of EA on the risk of long-term mortality (HR = 1.20, 95% CI: 0.81-1.78, p = 0.37).

4. DISCUSSION

Our analysis did not support the hypothetical benefits of perioperative EA in long-term cancer control or survival in patients

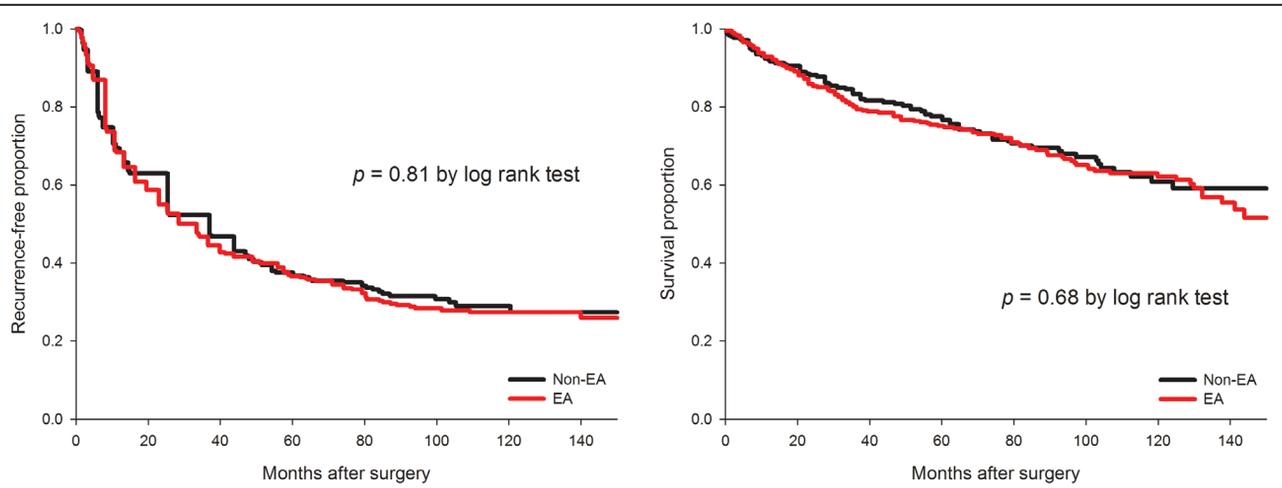

Fig. 2 Kaplan–Meier curves for cancer recurrence and overall survival of epidural analgesia (EA) and non-EA groups. No significant difference in cancer recurrence or overall survival after surgery was found between EA with non-EA groups.

Table 2

Univariate analysis of cancer recurrence and all-cause mortality after surgery

	Cancer recurrence			All-cause mortality		
	HR	95% CI	*p*	HR	95% CI	*p*
Epidural analgesia	1.02	0.85-1.23	0.814	1.06	0.80-1.39	0.682
Age	1.00	0.99-1.01	0.930	1.01	1.00-1.02	0.020
Sex (male vs female)	1.02	0.81-1.27	0.895	1.05	0.75-1.47	0.773
ASA class ≥ 3	0.99	0.80-1.23	0.938	1.65	1.23-2.20	0.001
HBsAg positive	1.23	1.00-1.50	0.048	0.94	0.70-1.25	0.667
Anti-HCV Ab positive	1.05	0.84-1.31	0.645	1.14	0.83-1.57	0.429
Alcoholism	0.87	0.57-1.32	0.516	0.94	0.51-1.72	0.832
Liver cirrhosis	1.35	1.12-1.62	0.001	1.48	1.13-1.93	0.005
Platelet count	1.00	1.00-1.00	0.384	1.00	1.00-1.00	0.151
INR	4.24	1.13-15.88	0.032	5.20	0.72-37.59	0.102
Total bilirubin ≥ 1.0 mg·dL^{-1}	1.01	0.80-1.28	0.902	1.21	0.87-1.68	0.250
AST > 40 IU/L	1.75	1.46-2.10	<0.001	1.99	1.52-2.62	<0.001
ALT > 40 IU/L	1.31	1.10-1.58	0.003	1.11	0.85-1.45	0.442
Alpha-fetoprotein > 20 ng·mL^{-1}	1.61	1.33-1.94	<0.001	1.40	1.06-1.84	0.018
Tumor diameter > 5 cm	1.72	1.43-2.07	<0.001	1.95	1.49-2.56	<0.001
Multiple nodules	1.70	1.38-2.08	<0.001	1.65	1.22-2.22	0.001
Microvascular invasion	1.79	1.47-2.19	<0.001	1.83	1.36-2.46	<0.001
Extracapsular invasion	1.39	1.15-1.67	<0.001	1.39	1.05-1.83	0.020
Anesthesia time*	1.61	1.30-2.00	<0.001	2.03	1.47-2.80	<0.001

ALT = alanine aminotransferase; Anti-HCV Ab = hepatitis C antibody; ASA = American Society of Anesthesiologists; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HR = hazard ratio; INR = international normalized ratio.
*On base-2 logarithmic scale.

following HCC resection. To the best of our knowledge, the current study is the first report to investigate the association between EA and cancer outcomes after resection surgery for HCC. This study provides valuable evidence to challenge the relationship between EA and HCC outcomes. There are two main strengths to this study. First, our analysis was based on a large cohort to increase the statistical power and obtain more reliable results. Second, multivariate proportional hazards models were used in combination with matching analysis to minimize potential confounding effects.

Table 3

Multivariable analysis of cancer recurrence and all-cause mortality after surgery before matching

	HR	95% CI	*p*
Recurrence-free survival			
Epidural analgesia	0.97	0.80-1.17	0.719
HBsAg positive	1.12	0.91-1.38	0.303
Liver cirrhosis	1.33	1.10-1.62	0.004
INR	0.87	0.21-3.51	0.843
AST > 40 IU/L	1.47	1.15-1.88	0.002
ALT > 40 IU/L	1.00	0.79-1.26	0.989
Alpha-fetoprotein > 20 ng·mL^{-1}	1.38	1.13-1.68	0.001
Tumor diameter > 5 cm	1.44	1.16-1.78	0.001
Multiple nodules	1.47	1.20-1.81	<0.001
Microvascular invasion	1.35	1.08-1.68	0.009
Extracapsular invasion	1.15	0.94-1.40	0.173
Anesthesia time*	1.22	0.96-1.55	0.101
Overall survival			
Epidural analgesia	0.95	0.71-1.26	0.714
Age	1.01	1.00-1.02	0.050
ASA class ≥ 3	1.41	1.04-1.91	0.029
Liver cirrhosis	1.46	1.10-1.94	0.008
AST > 40 IU/L	1.53	1.15-2.04	0.004
Alpha-fetoprotein > 20 ng·mL^{-1}	1.26	0.94-1.68	0.120
Tumor diameter > 5 cm	1.61	1.20-2.16	0.002
Multiple nodules	1.39	1.01-1.92	0.041
Microvascular invasion	1.42	1.02-1.98	0.039
Extracapsular invasion	1.09	0.81-1.47	0.557
Anesthesia time*	1.62	1.14-2.30	0.008

ALT = alanine aminotransferase; Anti-HCV Ab = hepatitis C antibody; ASA = American Society of Anesthesiologists; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; EA = epidural analgesia; HR = hazard ratio; INR = international normalized ratio.
*On base-2 logarithmic scale.

In recent decades, perioperative management has been increasingly considered to be an important factor affecting the morbidity and mortality of surgical patients. Since immune function is the major determinant of cancer progression, interventions altering the immune response during surgery may have an impact on postoperative cancer outcomes. Regional anesthetic techniques reduce the consumption of opioids, a potential immunosuppressant, which has therefore been hypothesized to be beneficial in decreasing cancer recurrence following curative-intent resection surgery.[11]

A previous study reported that the effect of regional analgesia on cancer outcomes was inconsistent, and that it may depend on the specific tumor type.[11] Previous in vitro studies have reported reduced proliferation of an aggressive cancer cell line and increased antiinflammatory cytokine concentrations in serum from breast cancer patients receiving regional anesthesia.[15,16] In addition, Gupta and coworkers reported a reduction in all-cause mortality in patients who received epidural anesthesia after rectal cancer resection.[17] Similarly, Christopherson and colleagues reported that the use of EA improved survival by up to 1.46 years among patients with nonmetastatic colon cancer.[18] However, in the Multicenter Australian Study of Epidural Anesthesia and Analgesia in Major Surgery (MASTER) trial, EA did not reduce the risk of death at 30 days or major postsurgical morbidity in high-risk patients undergoing major abdominal surgery.[19] Moreover, one study of long-term prospective follow-up of randomized controlled trials showed that the use of epidural block was not associated with cancer-free survival in major abdominal surgery.[20]

The perioperative use of EA has been shown to be safe and effective in offering adequate pain relief following open liver surgery.[21] In addition, EA has been shown to reduce the length of mechanical ventilation and hospital stay in cirrhotic patients undergoing liver resection without complications related to epidural catheter implantation or removal.[22] However, relatively few studies have investigated the effect of epidurals on cancer outcomes in patients with HCC. One retrospective study showed that in patients undergoing radiofrequency ablation for

small HCC, general anesthesia was associated with a lower risk of cancer recurrence compared with EA.[12] In that study, general anesthesia provided sufficient anesthesia and analgesia for the operators to maintain adequate intensity and duration of coagulation for radiofrequency ablation, which may have contributed to better cancer control.[12] In addition, general anesthesia can reduce systolic blood pressure and hepatic blood flow, which may increase the ablation diameter.[23] In the current study, epidurals were unlikely to have affected the surgical extent of HCC resection; however, it was unclear whether the patients who received EA had lower intraoperative systemic blood pressure and hence a greater use of fluids and blood products, which may have suppressed host defense mechanisms and increased the risk of postoperative cancer recurrence.[24] Moreover, in patients with HCC, relevant medical problems such as cirrhosis-related coagulopathy may contraindicate the use of epidurals, and this may result in selection bias. However, these potential confounders would bias the association away from the null and so are unlikely to change the conclusions.

There are several limitations to this study. First, this is a retrospective study and not a randomized control trial; hence, it is susceptible to bias and confounding variables. Although the surgical techniques remained unchanged during the study period at our hospital, other potential confounding factors may have biased the study results. Second, patients who died were not recorded in the database if they died at home or other hospitals, which made it difficult to determine their exact causes of death. Third, records of opioid and nonopioid analgesics, which may impact immune responses and oncologic outcomes, were not incorporated into the analysis due to data availability.

In conclusion, our results did not support a definite association between EA and cancer recurrence or OS in our patients with primary nonmetastatic HCC following surgical resection. Prospective studies are warranted to elucidate the relationship between EA and cancer outcomes in patients with HCC following surgery.

ACKNOWLEDGMENTS

This work was supported by grants from Taipei Veterans General Hospital (V104C-096), Taipei, Taiwan, ROC; Ministry of Science and Technology (MOST104-2314-B-075-015), Taipei, Taiwan, ROC, and Anesthesiology Research and Development Foundation (ARDF10401), Taipei, Taiwan, ROC.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A15.

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