

# BMJ Open Effect of epidural analgesia on cancer prognosis after colon cancer resection: a single-centre cohort study in Taiwan

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## ABSTRACT

**Objectives** Whether epidural analgesia affects cancer outcomes remains controversial. Most previous investigations ignored the confounding potential of important pathological factors on cancer outcomes. This study aimed to assess the association between epidural analgesia and cancer recurrence or death after resections for colon cancer.

**Design** Retrospective cohort study.

**Setting** A single-medical centre in Taiwan.

**Participants** Patients with stage I through III colon cancer undergoing bowel resection and receiving either epidural analgesia or intravenous opioid analgesia from 2005 to 2014.

**Primary and secondary outcome measures** Primary outcome was postoperative recurrence-free survival and secondary outcome was overall survival.

**Results** A total of 2748 and 1218 patients were analysed before and after propensity score matching. Cox regression analyses did not demonstrate any association between epidural analgesia and recurrence or death after matching (HR 0.89, 95% CI 0.65 to 1.21 for recurrence; 0.72, 95% CI 0.48 to 1.09 for death). Independent prognostic factors for cancer recurrence and death were higher level of preoperative carcinoembryonic antigen, perioperative blood transfusion, advanced cancer stage and pathological lymphovascular invasion.

**Conclusions** No definite association was found between epidural analgesia and risk of recurrence or death in patients undergoing colon cancer resection.

## INTRODUCTION

In 2018, approximately 1 850 000 new cases of colorectal cancer were diagnosed worldwide, and 881 000 died of colorectal cancer.<sup>1</sup> Colorectal cancer is ranked as the second most common cause of cancer death and poses a significant economic and healthcare burden globally.<sup>1</sup> For localised colorectal cancer, surgical removal of primary tumour is the only curative treatment modality, but about one-third of patients with stage II and III diseases developed cancer recurrence after resection surgery, which significantly reduced their long-term survival.<sup>2</sup>

## Strengths and limitations of this study

- A large cohort with long follow-up time was used to improve statistical power for the evaluation of epidural effects on long-term outcomes after colon cancer resection.
- Important pathological prognostic factors were considered in the analysis to reduce potential confounding effects.
- Propensity score matching methodology was employed to correct imbalances in the collected variables.
- Effects of unrecorded confounders on colon cancer outcomes cannot be further evaluated.
- The generalisability of study results may be limited due to the single medical centre design.

Epidural analgesia (EA) has been commonly used for controlling acute pain during and after abdominal surgery. The decrease in the stress response by EA may ameliorate surgery-related immunosuppression and thereby protect patients from postoperative tumour metastases.<sup>3 4</sup> Furthermore, opioids suppress both cellular and humoral immunity in humans,<sup>5 6</sup> and EA may help preserve immune function and protect against tumour spread by reducing perioperative use of opioids. However, whether EA reduces cancer recurrence or mortality in colorectal cancer remains inconclusive, with benefits reported in some studies<sup>7–12</sup> but not in others.<sup>13–15</sup> Prior studies had limitations of small patient sample (<500 subjects using epidurals),<sup>7 8 11–15</sup> surgery performed before 2005,<sup>7–13 15</sup> and mixed groups of subjects for different cancer pathology.<sup>7 9 12 13</sup> Pathological features of specimen are the major prognostic determinants after curative-intent surgery in colorectal cancer.<sup>16</sup> Nevertheless, previous studies did not take a complete consideration of these critical pathological predictors and ignored their potentially confounding effects on cancer prognosis.<sup>7 9 12 13</sup>



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Accordingly, we performed this study to examine the impact of EA on oncological outcomes after colon cancer resection with a particular emphasis on the adjustment for major prognostic factors by a comprehensive review of pathology reports. Specifically, we tested the hypothesis that EA was linked to longer recurrence-free survival (RFS) and overall survival (OS) in patients with stage I through III colon cancer after primary tumour resection.

## METHODS

The electronic medical databank was used to identify patients undergoing tumour resection for histologically proven colorectal cancer at the medical centre between 2005 and 2014. Exclusion criteria were patients with missing data about clinical and pathological factors, non-adenocarcinoma, distant metastasis at the time of surgery, pathology-proven carcinoma in situ and follow-up time less than 30 days. Due to the obvious difference in cancer treatment strategies and short-term prognosis between colon cancer and rectal cancer,<sup>17</sup> we also excluded rectal cancer to increase the sample homogeneity (figure 1).

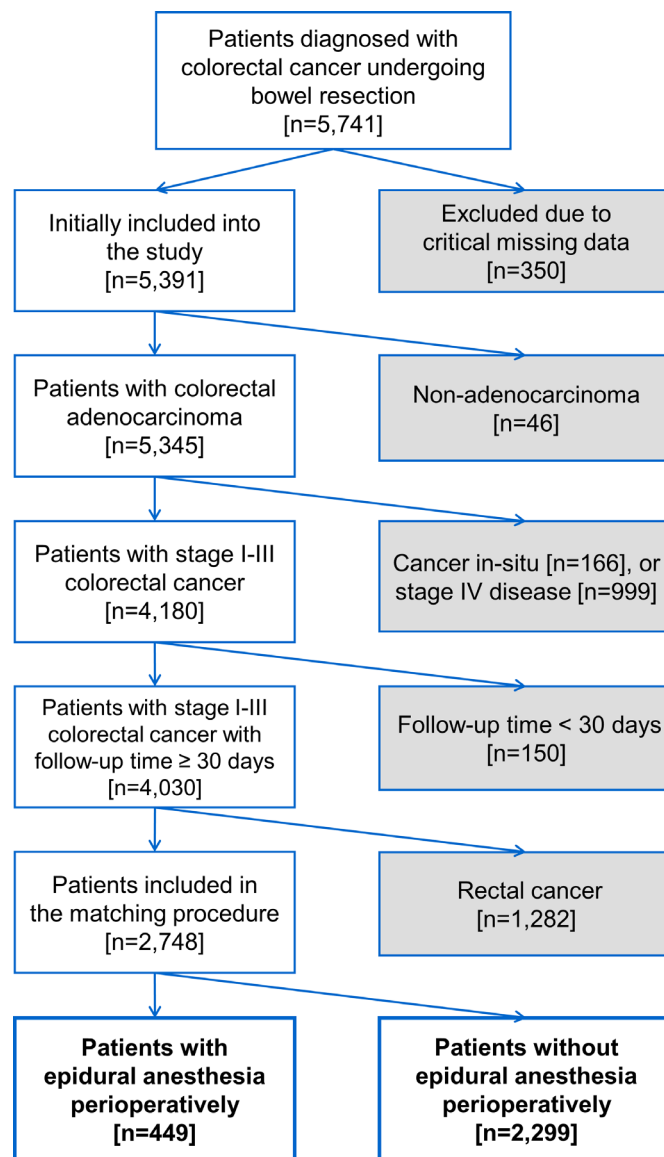
A total of 2748 patients were eligible for propensity score matching after meeting the selection criteria. Patients were classified into two groups: patients undergoing general anaesthesia with EA or without EA. The dataset of all the included patients was collected by a specialist anaesthesiologist. Specialist gastroenterologists were consulted when staging of cancer or time of recurrence was unclear in the medical records.

### Analgesic management

EA has been an integral part of postoperative pain control at this centre since 1990. Epidural catheter was typically placed at T10–T12 spine and tested before surgery. EA was given with a loading dose of lidocaine 60–100 mg before surgical incision and a basal infusion of bupivacaine 0.25% or 0.5% with or without fentanyl 1–2 µg/mL at a rate of 5–10 mL/hour. EA was typically continued for 48–72 hours for controlling postoperative pain. However, some patients undergoing bowel resection did not receive EA for the presence of contraindications to epidurals, ineffective epidurals or preference of patients or surgeons. Patients without epidurals would receive intravenous patient-controlled or as-needed opioid-based analgesia at the discretion of patients and anaesthesiologists.<sup>18</sup>

### Clinicopathological characteristics

The baseline attributes and potential predictor variables for cancer recurrence and mortality were derived from the medical record system as reported in our prior articles.<sup>19–22</sup> Clinical variables included demographics, pretreatment carcinoembryonic antigen (CEA) concentration,<sup>23</sup> perioperative use of packed red blood cells<sup>20 24 25</sup> and the use of preoperative or postoperative adjuvant chemotherapy or radiation therapy. Perioperative red cell transfusion was defined as any red cells given during



**Figure 1** Flow diagram for patient selection.

or within 7 days after surgery. Adjuvant chemotherapy (leucovorin and oxaliplatin or 5-fluorouracil; capecitabine; tegafur-uracil) or radiotherapy was defined as any treatment given within 90 days before or after surgery.

Pathological covariates comprised cell differentiation,<sup>16</sup> mucinous or signet-ring histology,<sup>26</sup> lymphovascular invasion<sup>27</sup> and perineural invasion.<sup>28</sup> Tumour nodes metastasis (TNM) staging was translated into stages I–III according to the American Joint Committee on Cancer (AJCC) criteria, seventh edition.<sup>29</sup> Tumour location was divided into right-sided tumour (cecum to splenic flexure), left-sided tumour (splenic flexure to sigmoid colon).<sup>30</sup>

### Outcome measurement

Primary outcome is RFS, defined as time from the date of surgery to the date of first cancer recurrence. Recurrence was determined by the presence of locoregional or metastatic lesions on imaging (plain radiography, spiral CT or MRI). Secondary outcome is OS, defined as time

from the date of surgery to the date of mortality. Each patient's status was determined by the medical record of outpatient surveillance or subsequent admissions. Data-sets were updated until 31 August 2016. For those without recurrence or death, survival times were considered as the corresponding censored observations.

### Statistical analysis

Comparisons of baseline attributes between epidural and non-epidural groups were performed using  $\chi^2$  tests for categorical covariates and either t-tests or Wilcoxon rank-sum tests for continuous covariates, as appropriate. Kaplan-Meier method was applied to compare the RFS and OS curves between groups. Univariate Cox regression analysis was used to assess the effect of covariates on recurrence-free or OS. Significant variables of recurrence-free or OS in univariate analysis were considered as candidates for stepwise model selection procedures in multivariable models. The association between EA and outcomes was further examined by adjusting for the determined predictors of the multivariable models.

To cope with the potential imbalance of measured confounders between two groups, propensity scores based on a list of patient characteristics was generated to estimate the probability of receiving epidurals<sup>31</sup> (online supplemental table 1). Propensity score analysis with 1:2 matching was conducted as the primary analysis to ensure sufficient balance in collected variables among matching groups. Stratified Cox regression analysis by matching groups was applied to examine the association between EA and cancer recurrence or OS. The significance level for all hypotheses was 0.05 for a two-tailed test. All the statistical analyses were performed using IBM SPSS Statistics, V.23.0 (IBM).

### Patient and public involvement

This study is a retrospective analysis using the institutional medical database. There was no patient involved in the recruitment to and conduct of the study.

## RESULTS

Among the included 2748 patients, 449 (16.3%) used EA. Median follow-up interval was 46.1 months (IQR 25.0–72.6). Note that patients receiving EA had longer follow-up interval and were more likely to have open surgery before matching (table 1). The proportion of epidural use decreased due to increasing use of laparoscopic technique for colon cancer resection at this centre in recent years. Online supplemental figure 1 shows the rate of epidural use in colon cancer resection significantly decreased from 2011 onwards. No significant difference in the cancer stage or pathological features was noted between groups (table 2). After propensity score matching, the final sample of 406 matched groups was analysed (tables 1 and 2).

### EA and recurrence risk

Before matching, the 3 years and 5 years RFS rates were 84.4% (95% CI 80.9% to 87.9%) and 80.9% (95%

CI 77.0% to 84.8%) in EA group and 82.2% (95% CI 80.4% to 84.0%) and 79.0% (95% CI 77.0% to 81.0%) in non-EA group, respectively. Note that EA was not associated with recurrence risk in the univariate analysis (HR 0.85,  $p=0.183$ ) (figure 2A).

Multivariable analysis identified eight independent prognostic factors of cancer recurrence, including preoperative CEA level (on base-10 logarithmic scale, HR=2.01), longer anaesthesia time (on base-2 logarithmic scale, HR=1.31), cancer stage (II vs I, HR=6.41; III vs I, HR=14.6), perioperative red cell transfusion (HR=1.48), signet-ring histology (HR=1.71), pathological lymphovascular invasion (HR=1.28), perineural invasion (HR=1.81) and preoperative chemotherapy and/or radiotherapy (HR=3.02). (table 3) The effect of EA on RFS after colon cancer surgery remained non-significant after the adjustment for these independent predictors (HR 0.85, 95% CI 0.65 to 1.10). After matching, stratified Cox regression model shows non-significant difference in the risk of cancer recurrence between groups (HR 0.89, 95% CI 0.65 to 1.21;  $p=0.449$ ). There was no significant association between EA and RFS in different subgroups of cancer stage (online supplemental table 2).

### EA and mortality risk

The 3 years and 5 years OS rates were 92.5% (95% CI 90.0% to 95.0%) and 87.2% (95% CI 83.7% to 90.7%) in EA group and 92.4% (95% CI 91.2% to 93.6%) and 87.9% (95% CI 86.1% to 89.7%) in non-EA group, respectively. No significant difference in postoperative OS was noted between groups ( $p=0.277$  by log rank test, figure 2B). In the univariate analysis, EA was not associated with mortality risk (HR=0.85,  $p=0.278$ ). Multivariable model identified 11 independent prognostic factors of OS, including older age (HR=1.03), male (HR=1.30), ASA class  $\geq 3$  (HR=1.82), heart failure (HR=1.60), chronic kidney disease (HR=1.44), preoperative CEA concentration (on base-10 logarithmic scale, HR=1.44), cancer stage (II vs I, HR=1.19; III vs I, HR=1.81), perioperative pRBC transfusion (HR=1.92), pathological lymphovascular invasion (HR=1.49), mucinous histology (HR=1.93) and radiotherapy (HR=2.67) (table 4). The effect of EA on OS after colon cancer surgery remained non-significant after the adjustment for these significant predictors (HR=0.76, 95% CI 0.56 to 1.03), similar to the results of stratified Cox regression model (HR=0.72, 95% CI 0.48 to 1.09;  $p=0.119$ ) after matching. Subgroup analyses showed EA was not associated with the risk of all-cause mortality in distinct cancer stages (online supplemental table 2).

## DISCUSSION

We found no definite evidence that EA was linked to better RFS or OS in colon cancer after primary tumour resection. Our study provided valuable evidence to challenge the association between EA and cancer outcomes with two strengths. First, our analysis was based on a large cohort to increase the statistical power and obtained

**Table 1** Patient demographic and clinical characteristics

	Before matching			After matching		
	EA group (n=449)	Non-EA group (n=2299)	Standardised difference	EA group (n=406)	Non-EA group (n=812)	Standardised difference
Age, year	69±14	68±13	8.0	69±14	69±13	3.8
Sex, male	288 (64.1%)	1409 (61.3%)	5.9	264 (65.0%)	523 (64.4%)	1.3
ASA class ≥3	170 (37.9%)	824 (35.8%)	4.2	155 (38.2%)	301 (37.1%)	2.3
BMI, kg/m <sup>2</sup>	24.1±3.7	24.1±3.8	0.7	24.1±3.7	24.0±3.7	3.0
<b>Comorbidities</b>						
Diabetes	85 (18.9%)	530 (23.1%)	10.1	81 (20.0%)	174 (21.4%)	3.6
Coronary artery disease	57 (12.7%)	295 (12.8%)	0.4	54 (13.3%)	110 (13.5%)	0.7
Heart failure	39 (8.7%)	156 (6.8%)	7.1	34 (8.4%)	59 (7.3%)	4.1
Stroke	22 (4.9%)	142 (6.2%)	5.6	21 (5.2%)	44 (5.4%)	1.1
Chronic kidney disease	61 (13.6%)	349 (15.2%)	4.5	58 (14.3%)	117 (14.4%)	0.4
Pretreatment CEA, µg/L	2.82 (2.16 to 4.62)	2.78 (2.00 to 5.57)	6.8	2.81 (2.16 to 4.61)	2.91 (2.06 to 6.01)	1.3
Anaesthesia time, min	270 (225 to 330)	285 (240 to 345)	18.7	270 (225 to 330)	270 (240 to 330)	10.4
Blood transfusion	127 (28.3%)	602 (26.2%)	4.7	113 (27.8%)	233 (28.7%)	1.9
Tumour location, right sided	199 (44.3%)	944 (41.1%)	6.6	174 (42.9%)	340 (41.9%)	2.0
Laparoscopic surgery	10 (2.2%)	215 (9.4%)	30.9	10 (2.5%)	22 (2.7%)	1.6
Preoperative C/T±R/T	2 (0.4%)	11 (0.5%)	0.5	2 (0.5%)	4 (0.5%)	0
Postoperative C/T (<90 days)	176 (39.2%)	1080 (47.0%)	15.8	156 (38.4%)	329 (40.5%)	4.3
Postoperative R/T (<90 days)	4 (0.9%)	8 (0.3%)	6.9	2 (0.5%)	4 (0.5%)	0
Follow-up interval, month	71.3 (37.8 to 120.7)	42.8 (24.3 to 66.8)	58.0	71.0 (37.8 to 101.1)	48.2 (27.7 to 73.0)	45.4

Values were mean±SD, counts (per cent) or median (IQR). Continuous variables were analysed with either t-tests or Wilcoxon rank sum tests, as appropriate; categorical variables were analysed with Pearson  $\chi^2$  tests. Standardised difference is the difference in mean, proportion or rank divided by the pooled SE, expressed as percentage. ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen; C/T, chemotherapy; R/T, radiotherapy.

**Table 2** Cancer staging and pathological features

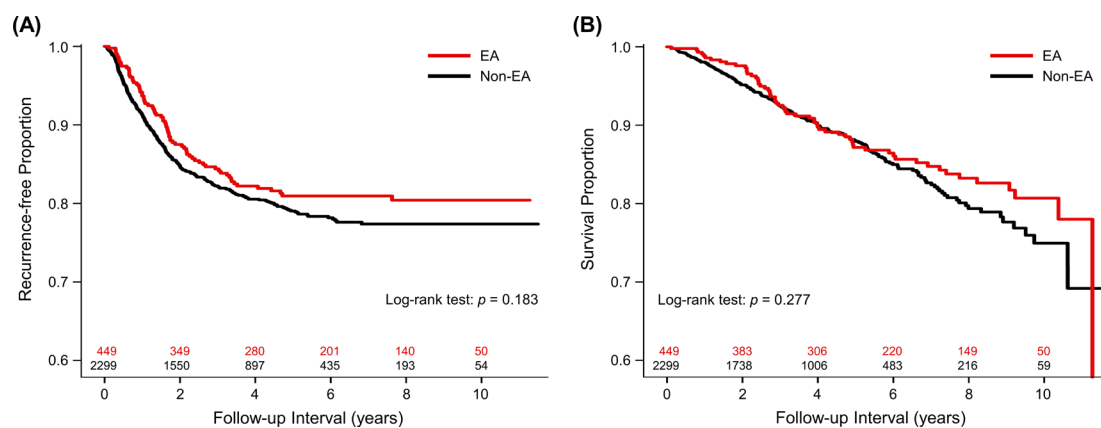
	Before matching			After matching		
	EA group (n=449)	Non-EA group (n=2299)	Standardised difference	EA group (n=406)	Non-EA group (n=812)	Standardised difference
AJCC stage			0.7			1.8
Stage I	97 (21.6%)	500 (21.7%)		91 (22.4%)	175 (21.6%)	
Stage II	190 (42.3%)	977 (42.5%)		175 (43.1%)	374 (46.1%)	
IIA	181 (40.3%)	879 (38.2%)		167 (41.1%)	347 (42.7%)	
IIB	6 (1.3%)	74 (3.2%)		5 (1.2%)	15 (1.8%)	
IIC	3 (0.7%)	24 (1.0%)		3 (0.7%)	12 (1.5%)	
Stage III	162 (36.1%)	822 (35.8%)		140 (34.5%)	263 (32.4%)	
IIIA	5 (1.1%)	63 (2.7%)		4 (1.0%)	19 (2.3%)	
IIIB	128 (28.5%)	591 (25.7%)		109 (26.8%)	196 (24.1%)	
IIIC	29 (6.5%)	168 (7.3%)		27 (6.7%)	48 (5.9%)	
Pathological features						
Tumour differentiation			0.03			1.4
Good	36 (8.1%)	174 (7.6%)		33 (8.1%)	64 (7.9%)	
Moderate	379 (84.8%)	1958 (85.7%)		345 (85.0%)	701 (86.3%)	
Poor	32 (7.2%)	153 (6.7%)		28 (6.9%)	47 (5.8%)	
Mucinous histology	22 (4.9%)	97 (4.3%)	3.2	18 (4.4%)	35 (4.3%)	0.6
Signet-ring histology	15 (3.4%)	61 (2.7%)	4.1	13 (3.2%)	20 (2.5%)	4.5
Lymphovascular invasion	57 (12.8%)	455 (19.9%)	19.5	50 (12.3%)	113 (13.9%)	4.7
Perineural invasion	17 (3.8%)	192 (8.4%)	19.3	15 (3.7%)	15 (1.8%)	11.3

Values were counts (per cent). Categorical variables are analysed with Pearson  $\chi^2$  tests. Standardised difference is the difference in mean, proportion or rank divided by the pooled SE, expressed as percentage. AJCC, American Joint Committee on Cancer; EA, epidural analgesia.

more reliable results. Second, propensity score matching method based on a comprehensive collection of predictors was applied to minimise potential confounding effects and selection bias.

Retrospective studies reported that EA was associated with longer OS in patients with non-metastatic colorectal cancer.<sup>7 10 12</sup> Other studies suggested benefits of EA to survival in specific populations (patients with rectal cancer

or ASA class three or 4).<sup>9 11</sup> So far, available literature refuted reduction in cancer recurrence after colorectal cancer surgery with EA.<sup>8 10 13–15</sup> The observed difference in OS may be potentially confounded by unmeasured predictors and our study fills this gap by incorporating more explanatory variables into the analysis. In a retrospective analysis, Warschkow *et al* reported that EA was associated with a reduced risk of postoperative pneumonia



**Figure 2** Kaplan-Meier curves for cancer recurrence and all-cause mortality of EA and non-EA groups with number of subjects at risk. No significant difference in cancer recurrence or all-cause mortality after colon cancer resection was found when comparing EA with non-EA groups. EA, epidural analgesia.

**Table 3** Forward model selection for recurrence-free survival before matching

	HR	95% CI	P value
Epidural analgesia	0.85	0.65 to 1.10	0.210
Pretreatment CEA*	2.01	1.71 to 2.36	<0.001
Anaesthesia time†	1.31	1.04 to 1.66	0.023
Blood transfusion	1.48	1.22 to 1.80	<0.001
AJCC stage			<0.001
II vs I	6.41	3.26 to 12.61	<0.001
III vs I	14.64	7.48 to 28.66	<0.001
Lymphovascular invasion	1.28	1.02 to 1.60	0.030
Perineural invasion	1.81	1.38 to 2.36	<0.001
Signet-ring histology	1.71	1.15 to 2.55	0.008
Preoperative C/T±R/T	3.02	1.24 to 7.34	0.015

\*On base-10 logarithmic scale.

†On base-2 logarithmic scale.

AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; C/T, chemotherapy; R/T, radiotherapy.

in patients undergoing open colorectal cancer surgery, but mortality rate was similar between epidural and non-epidural groups.<sup>32</sup> Meta-analysis has demonstrated that regional anaesthesia may protect against development of postoperative pulmonary complications in patients with chronic respiratory diseases.<sup>33</sup> Similarly, a multi-centre randomised controlled trial recently reported that regional anaesthesia and analgesia using paravertebral block reduced the risk of postoperative pulmonary

**Table 4** Forward model selection for overall survival before matching

	HR	95% CI	P value
Epidural analgesia	0.76	0.56 to 1.03	0.075
Age	1.03	1.02 to 1.04	<0.001
Sex (M vs F)	1.30	1.00 to 1.68	0.050
ASA class ≥3	1.82	1.38 to 2.40	<0.001
Heart failure	1.60	1.14 to 2.25	0.007
Chronic kidney disease	1.44	1.09 to 1.89	0.010
Pretreatment CEA*	1.44	1.13 to 1.83	0.003
Blood transfusion	1.92	1.49 to 2.48	<0.001
AJCC Stage			0.001
II vs I	1.19	0.80 to 1.77	0.379
III vs I	1.81	1.22 to 2.70	0.003
Lymphovascular invasion	1.49	1.12 to 1.98	0.006
Mucinous histology	1.93	1.25 to 2.99	0.003
Postoperative R/T	2.67	1.08 to 6.64	0.034

\*On base-10 logarithmic scale

AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; C/T, chemotherapy; F, female; M, male; R/T, radiotherapy.

complications but not recurrence or mortality in breast cancer after curative surgery compared with systemic opioid therapy.<sup>34</sup>

In addition to clinical features, pathological examination of the resected specimen is the most powerful tool for predicting prognosis after curative-intent surgery of colorectal cancer.<sup>16</sup> Previous reports were only adjusted for TNM or AJCC stages and tumour differentiation at most.<sup>7–13 15</sup> In fact, microscopic lymphovascular and perineural invasion have been proved to be important predictors of cancer recurrence and all-cause mortality in colorectal cancer.<sup>16 27 28</sup> In our analysis, microscopic lymphovascular invasion independently increased risk of cancer recurrence and all-cause mortality. Moreover, AJCC has recommended including pretreatment serum CEA levels (C stage) into the conventional TNM staging system of colorectal cancer.<sup>23</sup> Our study also demonstrated pretreatment CEA level as an independent predictor for colon cancer recurrence and support routine preoperative CEA testing on diagnosis of colon cancer.

Attention to some limitations of this study is needed. First, the effects of unrecorded confounders cannot be further evaluated, including use of opioids, conversion from laparoscopic to open surgery, surgical margin, genetic mutations of tumour, types and cycles of chemotherapy, and additional treatments for subsequently developed recurrence. Notably, our previous study showed no definite association between morphine consumption within 72 hours after surgery and long-term cancer outcome in patients with colorectal cancer using intravenous patient-controlled analgesia.<sup>35</sup> Second, the procedure of propensity score matching resulted in a loss of patient sample and statistical power. Third, the follow-up time for patients treated with EA was significantly longer than for patients without EA, which may possibly lead to outcome assessment bias. Nevertheless, the chance of colon cancer recurrence is greatest within 5 years after surgical resection.<sup>36</sup> In our study, patients followed up for more than 6 years in the non-EA group was obviously outnumbered those in the EA group (435 vs 201, [figure 1](#)) and reliable estimated results can still be obtained in the context of survival analysis. Fourth, as laparoscopic surgery is increasingly adopted, use of epidurals may become less for patients undergoing tumour resection for colorectal cancer.<sup>37</sup> However, EA has been reported to be effective in improving postoperative organ function and ambulation, relieving postsurgical pain, reducing postoperative pulmonary complications and facilitating postoperative recovery.<sup>32–34 38</sup> Based on the evidence, EA may remain a useful and beneficial treatment modality for postoperative recovery even for patients undergoing laparoscopic surgery. Finally, this study was conducted at a single medical centre and the generalisability to other places awaits more investigation.

## CONCLUSION

In conclusion, there was no definite association between epidural use and cancer recurrence or all-cause mortality in patients after colon cancer resection. More evidence is

required to confirm or refute this finding, pending the results of ongoing clinical trials.

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**Patient consent for publication** Not required.

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**Data availability statement** No data are available. Data are available on reasonable request but the approval of institutional review board will be necessary. Please contact the corresponding author for detail.

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