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Does postoperative morphine consumption for acute surgical pain impact oncologic outcomes after colorectal cancer resection?

A retrospective cohort study

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Abstract

Introduction: Whether morphine used in human cancer surgery would exert tumor-promoting effects is unclear. This study aimed to investigate the effects of morphine dose on cancer prognosis after colorectal cancer (CRC) resection.

Methods: In a retrospective study, 1248 patients with stage I through IV CRC undergoing primary tumor resections and using intravenous patient-controlled analgesia for acute surgical pain at a tertiary center between October 2005 and December 2014 were evaluated through August 2016. Progression-free survival (PFS) and overall survival (OS) were analyzed using proportional hazards regression models.

Results: Multivariable analysis demonstrated no dose-dependent association between the amount of morphine dose and PFS (adjusted hazard ratio, HR = 1.31, 95% confidence interval, CI = 0.85–2.03) or OS (adjusted HR = 0.86, 95% CI = 0.47–1.55). Patients were further classified into the high-dose and low-dose groups by the median of morphine consumption (49.7 mg), and the morphine doses were mean 75.5 ± standard deviation 28.8 mg and 30.1 ± 12.4 mg in high-dose and low-dose groups, respectively. Multivariable models showed no significant difference in PFS or OS between groups, either (adjusted HR = 1.24, 95% CI = 0.97–1.58 for PFS; adjusted HR = 1.01, 95% CI = 0.71–1.43 for OS).

Conclusion: Our results did not support a definite association between postoperative morphine consumption and cancer progression or all-cause mortality in patients following CRC resection.

Abbreviations: ASA = American Society of Anesthesiologists, CEA = carcinoembryonic antigen, CRC = colorectal cancer, IVPCA = intravenous patient-controlled analgesia, OS = overall survival, PFS = progression-free survival, SAS = Statistics Analysis System.

Keywords: cancer surgery, metastasis, opioid, recurrence

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1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the United States.[1] In 2018, approximately 1,850,000 new cases were diagnosed worldwide, and 881,000 died of CRC, accounting for approximately 9% of all cancer deaths.[2] Surgical resection is the primary treatment modality for stage I through III CRC; even in stage IV disease, hepatic resections with adjuvant chemotherapy may improve the clinical outcomes in selected patients.[3] However, cancer relapse plays a major role in determining the survival in patients following resection surgery, with a rate of 32.9% reported for stage II and III CRC.[4]

Morphine is one of the most frequently used narcotics for relieving postoperative acute pain and is one of the basic drugs for chronic cancer pain.[5] However, it has been shown to suppress the activity of natural killer cells in humans.[6] Besides, morphine in clinically relevant doses may stimulate tumor neovascularization and accelerate tumor progression in animal models.[7] Opioids may promote tumor growth by activating the mu-opioid receptor. Higher mu-opioid receptor expression and higher opioid requirement were independently linked to poor cancer outcomes in patients with metastatic prostate cancer.[8]

The effect of morphine dose on cancer outcomes is relatively unexplored in clinical settings, and most of previous studies focused on the opioid dose in the intraoperative period[9–11] or for chronic cancer pain.[8,12] Morphine is a commonly used analgesic during and after cancer surgery and the possibility of prometastatic properties of morphine could have a significant impact on postoperative pain management and cancer control.

Considering few studies focused on the effect of opioid dose for acute surgical pain on cancer relapse, we conducted the retrospective cohort study in patients following resection surgery for CRC to analyze the association between postoperative morphine requirements and cancer progression or all-cause mortality applying proportional hazards regression models. We hypothesized that morphine dose was associated with the risk of cancer progression and all-cause mortality following CRC resections.

2. Methods

2.1. Criteria for patient inclusion

After obtaining the approval by the Institutional Review Board (IRB-TPEVGH No. 2015-11-010CC), we reviewed the medical records of all patients undergoing bowel resection for histologically proven CRC at the tertiary center between January 2005 and December 2014. A total of 5741 patients were identified in the electronic medical databank, and 350 patients were excluded due to missing data about demographics or clinicopathologic predictors. Also, 166 patients with pathology-proven carcinoma in situ, and 46 patients with nonadenocarcinoma were excluded; 150 patients were excluded due to follow-up time less than 30 days. To reduce the heterogeneity in pain management and facilitate quantifying the morphine consumption for acute surgical pain, we excluded the 3776 patients not using intravenous patient-controlled analgesia (IVPCA). Finally, 5 patients with missing data about morphine dose were excluded. A total of 1248 patients were selected for further analyses after the exclusion processes.

2.2. Settings of intravenous patient-controlled analgesia

For postoperative pain control, morphine was the main opioid used in cancer surgery at this hospital. IVPCA was typically administered by an ambulatory infusion pump (Gemstar Yellow, Hospira, IL) programmed to deliver morphine continuously with infusion rates of 0.5 to 1.0 mg hr^{-1} and boluses of 1 mg with a lockout time of 6 minutes.[13,14] The pain service team followed the response of patients receiving IVPCA on a daily basis, and if there were adverse effects of morphine (e.g., nausea, itchiness, and others) or inadequate pain control, the infusion rate or bolus dose of IVPCA would be adjusted accordingly. In most patients, IVPCA was continued for 48 to 72 hours after surgery and switched to oral acetaminophen or nonsteroidal anti-inflammatory drugs thereafter. Patients who could not tolerate the adverse effects of morphine were given intravenous or oral acetaminophen or nonsteroidal anti-inflammatory drugs as alternative analgesics. We retrieved the data of total amount of in-hospital morphine consumption following CRC resection for each patient from the infusion pumps.

2.3. Clinical and pathologic covariates

The baseline attributes and risk factors for progression and mortality in CRC were derived from the electronic medical database as reported in our previous studies.[11,15] Clinical covariates were demographics, pretreatment concentration of carcinoembryonic antigen (CEA),[16] perioperative blood transfusion,[17] and records of adjuvant anticancer therapy. Perioperative blood transfusion was defined as any transfusions of allogeneic red blood cells given either during surgery or within 7 days after surgery. Adjuvant therapy was given in the form of chemotherapy (leucovori and oxaliplatin or fluorouracil, capecitabine, tegafur–uracil for stage II or III diseases; folfox- or irinotecan-based for stage IV diseases) or radiotherapy. Any adjuvant therapy was defined as administered within 90 days of surgery.

A collection of pathologic features was derived from a comprehensive review of pathological reports, including tumor differentiation, mucinous or signet-ring histology,[18] lymphovascular invasion,[19] and perineural invasion.[20] Tumor nodes metastasis stages were translated into stages I to IV based on the American Joint Committee on Cancer criteria, 7th edition.[21] Tumor location was classified into right-sided tumor (cecum to splenic flexure) or left-sided tumor (splenic flexure to rectum). The data were extracted by anesthesiologists not participating in the data analysis.

2.4. Primary and secondary outcomes

The primary outcome was progression-free survival (PFS), which was defined as the time from the date of surgery to the date of first cancer progression. Cancer progression is defined by the presence of locoregional or metastatic deposits detected by plain films, computerized tomography, magnetic resonance imaging, or positron-emission tomography.[22]

The secondary outcome was overall survival (OS), defined as the time from the date of surgery to the date of death. The date of death was determined based on medical records or death certificate. For patients without the event of cancer relapse or death, their survival times were processed as the corresponding censored observations with the last visit date used as the censored date. Patients were followed up until the end of August 2016.

2.5. Sample size estimation

Zylla and colleagues reported that for every 5 mg oral morphine equivalents per day, increase in opioid requirement elevated the risk of progression by 8% (hazard ratio, HR = 1.08, 95% confidence interval, CI = 1.03–1.13, $P < .001$) and the risk of death by 5% (HR = 1.05, 95% CI = 1.00–1.10, $P = .031$) in advanced prostate cancer.[8] In our study, high-dose group had higher intravenous morphine consumption than low-dose group by 45.4 mg, around equal to 45.4 mg oral morphine equivalents per day (assuming patients using IVPCA for 3 days after surgery). According to Schoenfeld formula for the sample size estimation of proportional hazards models,[23] at least 224 events were needed to attain a power of 0.8 assuming a type I error rate of 0.05, relative hazard of death 1.454, and the proportion of high-dose group in this study, 50.0%. Of note, we collected about 1.5 folds the minimum requirement (337 events in the entire cohort, 190 and 147 in high- and low-dose groups, respectively) to increase the statistical power of our study.

2.6. Statistical analysis

The comparisons of patient characteristics between groups were analyzed using chi-square tests for categorical variables and

either *t* tests or Wilcoxon rank sum tests for continuous variables, as appropriate. Kaplan–Meier method and log-rank test were used to compare survival distributions between groups. Patients without progression or death were censored at the end of follow-up time.

Morphine dose was regarded either as a dichotomous or a continuous variable in the survival analyses. The association between the amount of morphine dose and risks of cancer progression or all-cause mortality was analyzed using Cox proportional hazards regression models. The covariates significantly associated with PFS or OS in the univariate models were incorporated into the multivariable models to adjust for potential confounding effect. Stratified analysis by cancer stages was also conducted. A 2-sided significance level of 0.05 was used to define statistically significant difference. All the statistical analyses and plotting were conducted using Statistics Analysis System, Version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

A total of 1248 patients were selected for further analyses. In these patients, the minimum and maximum morphine dosages were 0.6 and 500.0 mg, respectively, and the interquartile range of morphine dose was from 30.8 to 70.3 mg. The median of morphine dose in the postoperative period was 49.7 mg and this number was subsequently used to separate patients into the high-dose and low-dose groups. The differences in the means of morphine dose between groups were 45.4 mg ($P < .001$).

The high-dose group was more likely to be younger, male and have higher body mass index (BMI), neoadjuvant chemotherapy or radiotherapy, and adjuvant chemotherapy. Besides, high-dose group has lower pretreatment CEA concentration and lower proportion of coronary arterial disease, heart failure, chronic kidney disease, perioperative blood transfusion, and laparoscopic surgery (Table 1). With regard to the pathologic features, high-dose group has more advanced cancer and higher proportion of mucinous histology (Table 2).

3.1. Morphine dose and cancer progression

The dose-dependent association between the amount of morphine dose and PFS was nonsignificant in the univariate analysis. However, high-dose group has significant shorter PFS than low-dose group in the univariate analysis (HR = 1.27, 95% CI = 1.03–1.58, $P = .029$ by log-rank test). Univariate analysis revealed several significant risk factors of cancer progression (Table 3), including American Society of Anesthesiologists (ASA) class ≥3, chronic kidney disease, anemia, higher pretreatment CEA level, blood transfusion, longer anesthesia time, advanced stage, and others.

Multivariable models identified 7 independent risk factors for cancer progression, including ASA class ≥3 (HR = 1.46), pretreatment CEA level (on base-10 logarithmic scale, HR = 1.46), cancer stage (II vs I, HR = 2.98; III vs I, HR = 6.47; IV vs I, HR = 32.46), lymphovascular invasion (HR = 1.32), perineural invasion (HR = 1.52), neoadjuvant chemotherapy and/or radiotherapy (HR = 2.04), and postoperative radiotherapy (HR = 1.96) (Table 3). After taking these significant predictors into account, the effect of morphine dose on PFS was nonsignificant, either as a linear (adjusted HR = 1.31, 95% CI = 0.85–2.03) or a categorical variable (adjusted HR = 1.24, 95% CI = 0.97–1.58). The association between morphine dose and PFS in distinct cancer stages was not significant in multivariable models either (Table 4). Figure 1 showed the Kaplan–Meier curves for PFS of the 2 groups.

Table 1

Patient demographics.

	Low dose (N = 624)	High dose (N = 624)	*P*	All patients
Morphine dose, mg	30.1 ± 12.4	75.5 ± 28.8	<.001	52.8 ± 31.7
Age, yr	75.1 ± 11.2	64.1 ± 11.2	<.001	69.6 ± 12.4
Sex, male	329 (52.7%)	398 (63.8%)	<.001	727 (58.3%)
ASA class ≥ 3	301 (48.2%)	175 (28.0%)	<.001	476 (38.1%)
BMI, $kg \cdot m^{-2}$	23.6 ± 3.6	24.5 ± 3.7	<.001	24.0 ± 3.7
Comorbidites				
Diabetes	155 (24.8%)	160 (25.6%)	.745	315 (25.2%)
Coronary artery disease	107 (17.1%)	52 (8.3%)	<.001	159 (12.7%)
Heart failure	67 (10.7%)	26 (4.2%)	<.001	93 (7.5%)
Stroke	53 (8.5%)	40 (6.4%)	.161	93 (7.5%)
Chronic kidney disease	141 (22.6%)	76 (12.2%)	<.001	217 (17.4%)
Anemia	98 (17.9%)	75 (14.7%)	.163	173 (13.9%)
Pretreatment CEA, $\mu g \cdot L^{-1}$	3.3 (2.2–8.6)	2.9 (2.0–7.5)	.022	3.1 (2.1–8.0)
Right-sided tumor	194 (31.1%)	183 (29.3%)	.498	377 (30.2%)
Laparoscopic surgery	55 (8.8%)	34 (5.4%)	.021	89 (7.1%)
Anesthesia time, min	293 (240–345)	300 (240–360)	.240	298 (240–360)
pRBC transfusion	181 (29.0%)	146 (23.4%)	.024	327 (26.2%)
Preoperative C/T ± R/T	41 (6.6%)	67 (10.7%)	.009	108 (8.7%)
Postoperative C/T	273 (43.8%)	356 (57.1%)	<.001	629 (50.4%)
Postoperative R/T	13 (2.1%)	18 (2.9%)	.363	31 (2.5%)
Year of procedure			<.001	
2005–2008	153 (12.3%)	248 (19.9%)		401 (32.1%)
2009–2011	221 (17.7%)	181 (14.5%)		402 (32.2%)
2012–2014	250 (20.0%)	195 (15.6%)		445 (35.7%)

Values were mean ± SD, median (interquartile range), or counts (percent). Continuous variables are analyzed with independent *t*-tests or Wilcoxon rank-sum tests, as appropriate; categorical variables are analyzed with Pearson chi-square tests. ASA = American Society of Anesthesiologists, BMI = body mass index, C/T = chemotherapy, CEA = carcinoembryonic antigen, pRBC = packed red blood cell, R/T = radiotherapy.

Table 2

Cancer stages and pathologic features.

	Low dose (N = 624)	High dose (N = 624)	*P*	All patients
AJCC stage			.029	
Stage I	144 (23.1%)	135 (21.6%)		279 (22.4%)
Stage II	219 (35.1%)	198 (31.7%)		417 (33.4%)
IIA	205 (32.9%)	184 (29.5%)		389 (31.2%)
IIB	9 (1.4%)	11 (1.8%)		20 (1.6%)
IIC	5 (0.8%)	3 (0.5%)		8 (0.6%)
Stage III	184 (29.5%)	176 (28.2%)		360 (28.8%)
IIIA	18 (2.9%)	20 (3.2%)		38 (3.0%)
IIIB	129 (20.7%)	134 (21.5%)		263 (21.1%)
IIIC	37 (5.9%)	22 (3.5%)		59 (4.7%)
Stage IV	77 (12.3%)	115 (18.4%)		192 (15.4%)
IVA	46 (7.4%)	72 (11.5%)		118 (9.5%)
IVB	31 (5.0%)	43 (6.9%)		74 (5.9%)
Pathologic features				
Tumor differentiation			.618	
Good	44 (7.1%)	41 (6.6%)		85 (6.8%)
Moderate	533 (85.4%)	544 (87.2%)		1077 (86.3%)
Poor	47 (7.5%)	39 (6.3%)		86 (6.9%)
Mucinous histology	22 (3.5%)	45 (7.2%)	.004	67 (5.4%)
Signet-ring histology	16 (2.6%)	21 (3.4%)	.396	37 (3.0%)
Lymphovascular invasion	144 (23.1%)	136 (21.8%)	.608	280 (22.4%)
Perineural invasion	57 (9.1%)	52 (8.3%)	.635	109 (8.7%)

Values were counts (percent). Categorical variables are analyzed with Pearson chi-square tests. AJCC = American Joint Committee on Cancer.

Table 3

Univariate analysis of cancer progression and all-cause mortality.

	Cancer progression			All-cause mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Morphine dose (binary)	1.27	1.03–1.58	.029	0.93	0.71–1.21	.582
Morphine dose (linear)	1.32	0.90–1.94	.156	0.83	0.53–1.30	.420
Age	1.00	0.99–1.00	.245	1.01	1.00–1.02	.044
Sex (M vs F)	0.97	0.78–1.20	.755	1.27	0.96–1.68	.089
ASA class $\geq$ 3	1.41	1.14–1.75	.002	1.88	1.44–2.46	<.001
BMI	0.98	0.95–1.01	.147	0.91	0.87–0.95	<.001
Diabetes	0.93	0.72–1.19	.554	1.05	0.78–1.43	.749
Coronary arterial disease	1.19	0.88–1.61	.255	1.02	0.69–1.52	.913
Heart failure	1.20	0.81–1.77	.358	1.39	0.86–2.26	.181
Stroke	1.19	0.80–1.76	.390	1.24	0.77–2.01	.378
Chronic kidney disease	1.37	1.05–1.78	.019	1.93	1.42–2.61	<.001
Anemia	1.47	1.02–2.11	.039	1.87	1.24–2.82	.003
Pretreatment CEA*	2.95	2.57–3.38	<.001	2.77	2.32–3.31	<.001
Laparoscopy surgery	0.73	0.46–1.16	.179	0.56	0.29–1.09	.088
Right- vs left-sided tumor	1.17	0.93–1.47	.175	1.39	1.05–1.84	.022
pRBC transfusion	2.27	1.83–2.83	<.001	3.29	2.52–4.30	<.001
Anesthesia time†	2.12	1.66–2.71	<.001	1.83	1.35–2.48	<.001
Preoperative C/T $\pm$ R/T	2.56	1.92–3.42	<.001	2.48	1.73–3.57	<.001
Postoperative C/T	5.48	4.16–7.24	<.001	2.68	2.00–3.60	<.001
Postoperative R/T	4.36	2.82–6.73	<.001	4.13	2.44–6.99	<.001
Year of procedure			.032			.052
2009–2011 vs 2005–2008	1.39	1.07–1.81	.013	1.31	0.96–1.79	.090
2012–2014 vs 2005–2008	1.09	0.83–1.44	.542	0.86	0.59–1.26	.437
Stage			<.001			<.001
II vs I	3.60	1.83–7.09	<.001	1.57	0.91–2.73	.108
III vs I	10.47	5.48–19.98	<.001	2.90	1.72–4.90	<.001
IV vs I	69.11	36.29–131.58	<.001	15.42	9.27–25.66	<.001
Tumor differentiation			<.001			.008
Moderate vs good	2.38	1.30–4.34	.005	1.53	0.83–2.81	.172
Poor vs good	5.20	2.66–10.15	<.001	2.92	1.39–6.14	.005
Mucinous histology	1.93	1.32–2.83	.001	1.62	0.97–2.70	.064
Signet-ring histology	2.04	1.24–3.38	.005	1.72	0.85–3.50	.131
Lymphovascular invasion	3.15	2.53–3.92	<.001	2.57	1.94–3.41	<.001
Perineural invasion	2.78	2.09–3.70	<.001	2.47	1.69–3.60	<.001

Morphine dose is considered as a linear or categorical variable (<49.7 or $\geq$ 49.7 mg). ASA = American Society of Anesthesiologists, BMI = body mass index, C/T = chemotherapy, CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, M = male, F = female, pRBC = packed red blood cell, R/T = radiotherapy.

* On base-10 logarithmic scale.

† On base-2 logarithmic scale.

Table 4

Multivariable analysis of cancer progression and all-cause mortality.

	HR	95% CI	P
Progression-free survival			
Morphine dose (binary)*	1.24	0.97–1.58	.083
Morphine dose (linear)	1.31	0.85–2.03	.217
ASA class ≥ 3	1.46	1.15–1.84	.002
Pretreatment CEA†	1.46	1.24–1.72	<.001
Stage			<.001
II vs I	2.98	1.46–6.07	.003
III vs I	6.47	3.06–13.69	<.001
IV vs I	32.46	15.08–70.06	<.001
Lymphovascular invasion	1.32	1.00–1.73	.049
Perineural invasion	1.52	1.08–2.12	.015
Preoperative C/T ± R/T	2.04	1.46–2.83	<.001
Postoperative R/T	1.96	1.23–3.13	.005
Overall survival			
Morphine dose (binary)‡	1.01	0.71–1.43	.957
Morphine dose (linear)	0.86	0.47–1.55	.607
ASA class ≥ 3	1.67	1.20–2.31	.002
BMI	0.94	0.90–0.98	.005
Pretreatment CEA†	1.56	1.23–1.97	<.001
pRBC transfusion	1.59	1.14–2.22	.006
Stage			<.001
II vs I	1.35	0.70–2.59	.373
III vs I	2.25	1.05–4.80	.037
IV vs I	8.54	3.88–18.80	<.001
Lymphovascular invasion	1.58	1.09–2.30	.015
Preoperative C/T ± R/T	2.15	1.38–3.36	<.001
Postoperative R/T	1.81	1.01–3.27	.048

Morphine dose is considered as a linear or categorical variable (<49.7 or ≥49.7 mg). ASA = American Society of Anesthesiologists, BMI = body mass index, C/T = chemotherapy, CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, pRBC = packed red blood cell, R/T = radiotherapy. *Stage I: $P = .106$, stage II: $P = .191$, stage III: $P = .683$, stage IV: $P = .332$; † on base-10 logarithmic scale; ‡ stage I: $P = .848$, stage II: $P = .333$, stage III: $P = .764$, stage IV: $P = .687$.

3.2. Morphine dose and all-cause mortality

The dose-dependent association between the amount of morphine dose and OS was not significant in the univariate analysis. The difference in OS was not significant between the high- and low-dose groups, either ($P = .582$). In the univariate analysis, variables associated with shorter OS were older age, ASA physical class ≥3, lower BMI, chronic kidney disease, higher pretreatment CEA level, longer anesthesia time, anemia, blood transfusion, right-sided tumor, advanced cancer stage, etc (Table 3). Multivariable analysis demonstrated 8 independent prognostic determinants for OS, including ASA class ≥3 (HR = 1.67), BMI (HR = 0.94), higher pretreatment CEA concentration (on base-10 logarithmic scale, HR = 1.56), perioperative blood transfusion (HR = 1.59), cancer stage (III vs I, HR = 2.25; IV vs I, HR = 8.54), lymphovascular invasion (HR = 1.58), neoadjuvant chemotherapy and/or radiotherapy (HR = 2.15), and postoperative radiotherapy (HR = 1.81) (Table 4). Adjusting for these covariates, no definite association between morphine dose and OS was noted, either as a linear (adjusted HR = 0.86, 95% CI = 0.47–1.55) or a categorical variable (adjusted HR = 1.01, 95% CI = 0.71–1.43) (Table 4). The stratified analysis by cancer stage showed similar results. Figure 2 showed the Kaplan–Meier curves for OS of the 2 groups.

4. Discussion

Our results did not support a definite association between morphine dose for acute pain management and oncologic outcomes following colorectal surgical resection. The association between postoperative morphine consumption and CRC outcomes was nonsignificant when the amount of morphine dose was regarded either as a linear or a binary variable. The stratified analysis by cancer stage demonstrated similar findings. Compared with the previous studies,[8–10,12,24] our analysis was based on a larger patient sample and incorporated important clinicopathologic prognostic factors into the multivariable models to provide more solid evidence to challenge the association between morphine dose and cancer outcomes in clinical settings.

In preclinical studies, the effect of morphine on tumor growth is mixed and conflicting. Morphine at clinically relevant doses increased angiogenesis and promoted breast tumor growth in mice.[7] However, the surgery-induced increase in tumor retention was attenuated by morphine in rats undergoing laparotomy.[25] The effect was greater when morphine was administered preoperatively. Besides, morphine was found to inhibit tumor growth and dissemination in rats with melanoma cells, which suggested that relief from cancer pain by morphine may suppress tumor growth and spread.[26] The conflicting

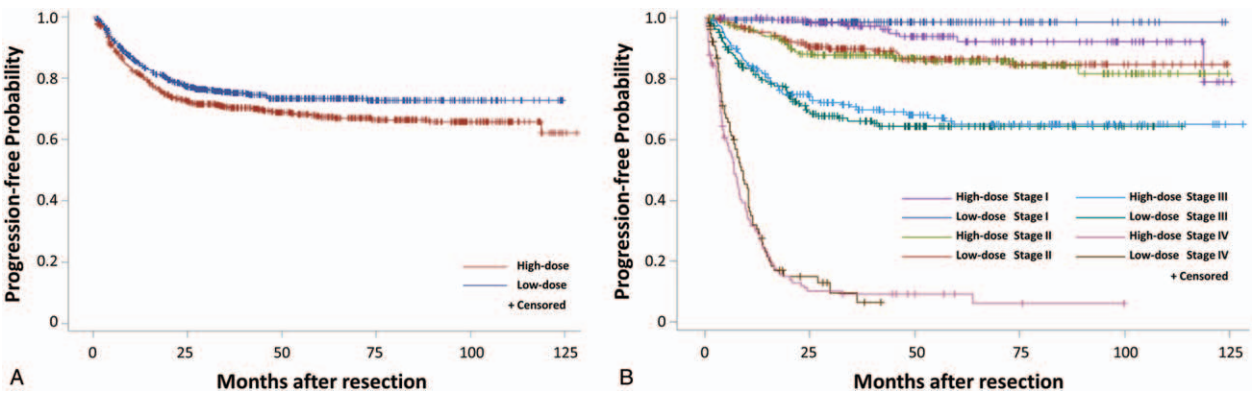

Figure 1. Kaplan–Meier curves for progression-free survival of the two groups. Significantly better progression-free survival after surgery was found for colorectal cancer in low-dose groups compared with high-dose group in all patients ($P = .028$ by log-rank test) (A) but not stage-stratified subgroups (B) in univariate analysis (stage I: $P = .107$, stage II: $P = .639$, stage III: $P = .590$, stage IV: $P = .529$; all by log-rank tests).

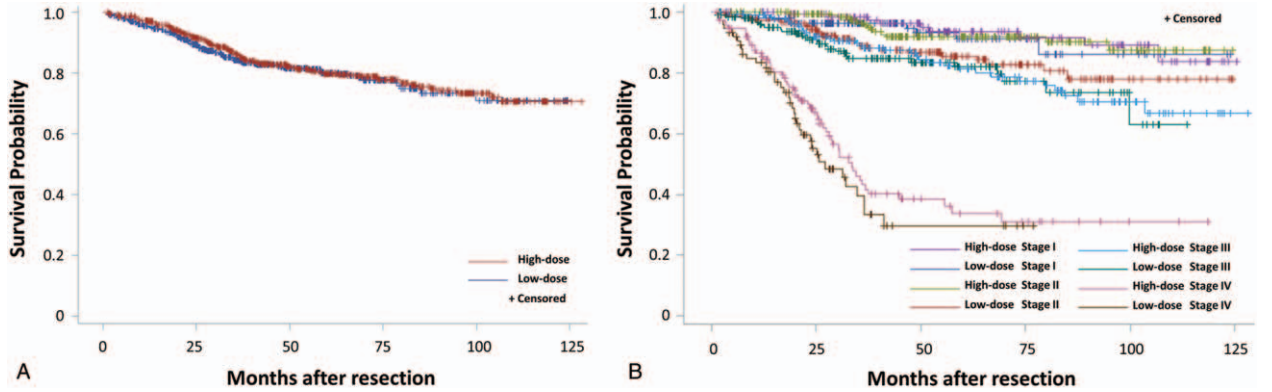

Figure 2. Kaplan–Meier curves for overall survival of the two groups. No significant difference of overall survival after surgery was found for colorectal cancer when comparing high-dose with low-dose groups in univariate analysis, except for stage II disease (all patients: $P = .583$, stage I: $P = .517$, stage II: $P = .014$, stage III: $P = .672$, stage IV: $P = .291$; all by log-rank tests).

findings in prior research may be explained by different types of cancer, the interaction between opioid dose and pain-induced stress response, and their combined effects on immune system.

Furthermore, whether higher opioid dose has a detrimental effect on cancer outcomes is still inconclusive in humans. Most prior studies focused on the opioid dose in the intraoperative period. The administration of intraoperative sufentanil was reported to be associated with a higher risk of cancer recurring in patients with prostate cancer, but the dose–response relationship was not mentioned.[9] In nonsmall cell lung cancer, higher intraoperative opioid consumption was found to be a risk factor for shorter OS in stage I but not stage II or III diseases.[10] In our study, although the patients with stage II CRC were noted to have shorter OS in high-dose group in the univariate analysis, the association disappeared after adjusting for covariates. A retrospective study of 99 patients with nonsmall cell lung cancer revealed that increased opioid doses during initial 96 hours postoperative period were associated with higher recurrence risk within 5 years after surgery, but the association between intraoperative opioid dose and cancer recurrence was not significant.[24] Similarly, no definite association between the intraoperative fentanyl dose and recurrence rate was reported in patients undergoing colorectal resection surgery.[11] In our analysis, the patients with higher narcotic demand were more likely to be younger and healthier and have more advanced cancer stage compared with their counterparts. After considering other prognostic factors, the correlation between morphine dose and cancer outcomes was not significant, which suggested that factors increasing morphine demand (e.g., more aggressive tumor and more extensive tumor resection) affected postoperative progression and survival rather than the opioid dose itself.

Although several studies have reported the potential tumor-promoting effect of opioid in clinical settings, there was no clear risk threshold below which narcotics consumption being associated with low recurrence risk. Previous reports showed that mean dose of sufentanil 23 μg used intraoperatively in prostate cancer[9] and mean dose of oral morphine equivalents 232 mg given postoperatively in nonsmall cell lung cancer[24] may increase the risk of cancer recurrence compared with their counterparts. In our study, the analysis was performed on a larger cohort, and the mean and maximal consumptions of intravenous morphine were 75.5 and 500.0 mg in high-dose group (comparable with the opioid doses of these studies on an equianalgesic basis), but the multivariable models did not confirm a significant association between higher opioid requirements and risk of cancer progression.

The impact of chronic opioid requirements for cancer pain on the risk of cancer progression was also conflicting in the previous studies. In 209 patients with stage IIIB or IV nonsmall cell lung cancer, greater opioid requirements and severity of chronic cancer-related pain were reported to be independently associated with shorter survival.[12] Besides, greater opioid requirements and mu-opioid receptor expression were associated with increased risk of cancer progression and all-cause mortality in patients with metastatic prostate cancer.[8] However, a large prospective cohort study enrolling 34,188 patients showed no clinically relevant evidence of an association between narcotic prescriptions and breast cancer recurrence, regardless of opioid type, cumulative consumption, and chronicity of use.[27]

Several limitations are inherent in the study's retrospective design. First, this is not a randomized controlled trial, and the pain control and cancer treatment were not standardized. Second, it is difficult to assess potential confounding effects from unmeasured variables, including surgical techniques, extent of resection, regional analgesia, and others.[28] Third, our analysis did not take nonopioid analgesics into account due to the data availability of the medical databank. Presumably, patients with lower opioid consumption might be more likely to receive nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs or local anesthetics), which have been shown to exert anti-inflammatory effects and reduce the risk of cancer recurrence.[29] Hence, this potential confounder is supposed to bias the association away from the null and unlikely to change the conclusion.

In conclusion, our analysis did not support the association between postoperative morphine consumption for acute surgical pain and cancer progression or all-cause mortality in patients after CRC resection. Such findings have important clinical implications for postoperative pain management in cancer patients. Prospective studies are needed to clarify the correlation between postoperative opioid use and cancer prognosis.

Author contributions

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