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Association between Epidural Analgesia and Cancer Recurrence after Colorectal Cancer Surgery

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ABSTRACT

Introduction: Animal studies suggest that regional anesthesia and optimal postoperative analgesia independently reduce cancer metastasis. Retrospective clinical studies suggest reductions in recurrence of several cancer types in patients receiving perioperative neuraxial analgesia. Thus, the authors determined the association between perioperative epidural analgesia and cancer recurrence in patients undergoing colorectal cancer surgery.

Methods: After obtaining approval of institutional review board, the authors reviewed the records of 669 patients undergoing colorectal cancer surgery between January 2000 and March 2007. Follow-up ended in November 2008. The authors' primary outcome was time to cancer recurrence. Cox proportional hazards models were used.

Results: Two hundred fifty-six patients who received epidural analgesia and 253 who did not were analyzed in a multivariable model to assess the association between epidural use and cancer recurrence. Overall, no association between epidural use and recurrence was found ($P = 0.43$), with an adjusted estimated hazard ratio of 0.82 (95% CI 0.49–1.35). In *post hoc* analyses, epidural use was associated with a lower cancer recurrence in older patients (age older than 64 yr), but not in younger (interaction $P = 0.01$). A sensitivity analysis using propensity score analysis found similar results.

Conclusion: In contrast to previous retrospective studies in the colon, breast, and prostate cancer surgery, the authors found that the use of epidural analgesia for perioperative pain control during colorectal cancer surgery was not associated with a decreased cancer recurrence; however, a potential benefit was observed in older patients. The benefit of regional anesthesia on cancer recurrence may thus depend on the specific tumor type.

What We Already Know about This Topic

- Epidural analgesia after cancer surgery has been suggested in some retrospective reviews to reduce metastasis

What This Article Tells Us That Is New

- In a retrospective review of 669 patients undergoing colorectal cancer surgery, epidural analgesia did not reduce cancer overall occurrence
- Epidural analgesia was associated with reduced cancer occurrence in older subjects (older than 64 yr), suggesting an effect of age or tumor type

PRIMARY solid tumors can often be removed surgically; however, metastasis remains the cause of 90% of deaths.[1] Although potentially curative, surgery may actually contribute to metastasis: it suppresses immunity, facilitating the growth of preexisting micrometastases, and allows for dissemination of malignant cells during tumor manipulation.[2,3] Inhaled anesthetics and intravenous opioids may contribute to metastasis by decreasing the activity of natural killer (NK) cells. Morphine, in clinically relevant concentrations, stimulates cancer cell survival, cell cycle progression, and endothelial proliferation and angiogenesis.[4–6] In addition, morphine induces tumor neovascularization and increases tumor progression.[6] These results suggest that the clinical use of morphine could potentially be harmful in patients with angiogenesis-dependent cancers.

Epidural analgesia or anesthesia attenuates the surgical stress response and prevents the inhibition of the immune

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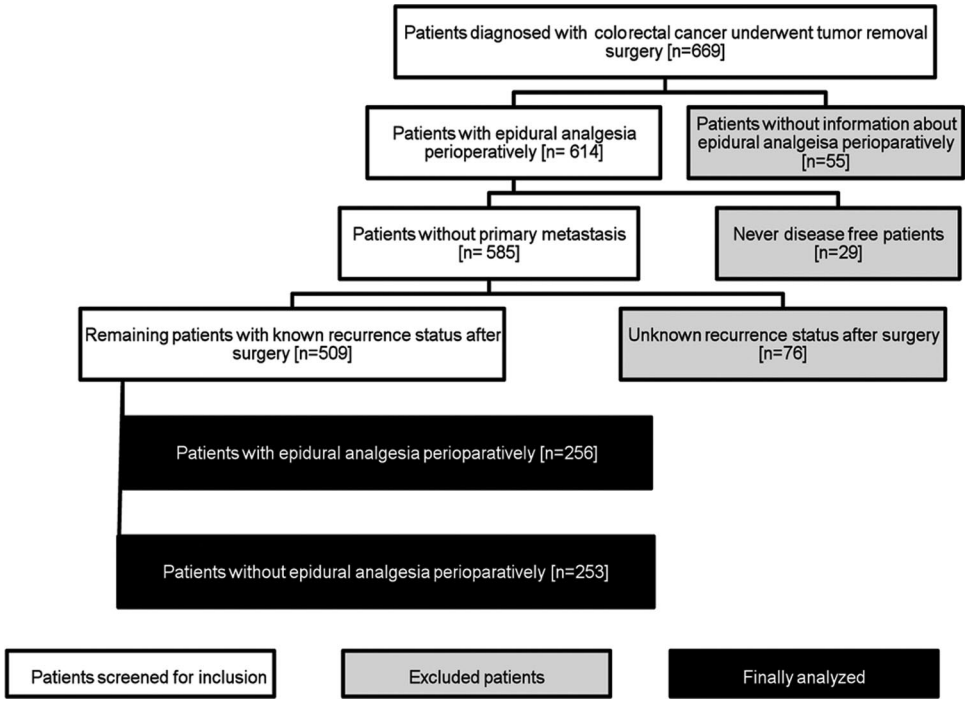

Fig. 1. Study overview.

system.[7] In addition, it decreases the requirement for inhaled anesthetics and opioids. When administered intrathecally in small quantities, opioids exert less immunosuppressive effects than after systemic administration.[7] Therefore, epidural analgesia may be beneficial for patients undergoing cancer surgery.

Three retrospective studies have suggested a reduction in cancer recurrence in patients receiving perioperative neuraxial analgesia.[8–10] Hence, we performed this retrospective trial that aimed to assess the association between perioperative epidural analgesia on cancer recurrence after colorectal cancer surgery. We hypothesized that when corrected for other covariates that represent known risk for cancer recurrence (*e.g.*, hypothermia and blood transfusion),[11,12] epidural analgesia/anesthesia would decrease the recurrence rate in patients with colorectal cancer presenting for surgical resection.

Materials and Methods

After approval from the Institutional Review Board (University of Virginia, Charlottesville, Virginia), we reviewed the records of 669 patients who underwent colorectal cancer surgery at the University of Virginia between January 2000 and March 2007. Follow-up ended in November 2008. We excluded patients for whom no information on intraoperative epidural use was available and those who were never disease-free or had unknown recurrence status after surgery (fig. 1). The decision to use epidural analgesia was made by the patient in consultation with the attending anesthesiologist. Our primary outcome was time to cancer recurrence, which was defined as time from the date of surgery to the date of cancer recurrence or date of last known tumor status (if no recurrence).

An electronic database was used to determine the baseline variables and risk factors for cancer recurrence, type of anesthesia, and date of surgery. Tumor nodes metastasis staging was also obtained from the record and translated into stages 0–IV using the pathologic staging system that was in use at the time the patients had their surgery.

All clinically relevant and possibly interacting factors for tumor outcome and progression were recorded in a database (table 1). The epidural and nonepidural groups were compared on all available potential confounders using Pearson chi-square test, Student *t* test, and Wilcoxon rank sum test, as appropriate. The relationship between intraoperative epidural use and cancer recurrence was first assessed univariably using Kaplan-Meier estimates of the survivor function and the log-rank test[13] and with Cox proportional hazards regression.

Our primary analysis was a multivariable Cox proportional hazards regression model[14] that assessed the relationship between epidural use (*vs.* not) and cancer recurrence, adjusting for potentially confounding perioperative variables. Baseline intraoperative and postoperative variables with significant effects ($P < 0.25$) on univariate analysis were considered for inclusion in a main-effect multivariable Cox model (model 1) through the use of backward selection (α-to-stay was set conservatively to 0.25 to adjust for confounding). In addition, a Cox model considering main effects and interactions (model 2) was fitted; all the main effects contained in model 1 were forced into the model, and all pairwise interactions between intraoperative epidural use and each main effect were considered.[15] Specifically, backward

selection was used with an interaction stay criterion of 0.10, considering all interactions that were univariably significant at 0.10, and retained noninteracting main effects if significant at 0.25.

Linearity of the relationship between each continuous covariable and outcome was assessed using *P*-spline regression.[16] The proportional hazards assumption of the Cox model was assessed for each covariable included in the model by visually assessing whether a plot of hazard *versus* logarithm of time was parallel for the comparison groups and by a Komolgorov-type supremum test.[17,18]

In addition, we performed a sensitivity analysis on our chosen method (*i.e.*, the above multivariable modeling) in which we adjusted for confounding using propensity score analysis. First, we estimated the probability of receiving epidural (*i.e.*, the propensity score) for each patient using logistic regression based on the values of all covariables included in model 1. Then we examined the association between colon cancer recurrence and epidural use in a Cox proportional hazards regression model while stratifying on the quintiles of propensity score.

The significance level for each main effect hypothesis was 0.05. No adjustment to the criterion for significance was made for assessing multiple outcome variables. SAS software version 9.1 (SAS Institute, Cary, NC) and the R statistical software version 2.7.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used for analyses.

Results

Comparisons between the epidural therapy (N = 256) and no epidural therapy (N = 253) groups on baseline, intraoperative, and postoperative factors are shown in table 1. Patients who received epidural therapy were more likely to be male, had a lower American Society of Anesthesiologists Score, a worse tumor grade, were more likely to have rectal cancer (compared with colon cancer), received different surgical procedures, were less likely to have emergent surgery, received lower intraoperative F_{IO_2}, received greater mean crystalloid volume, had a higher estimated blood loss but were less likely to be transfused, and were more likely to receive chemotherapy or radiation therapy.

Median (quartiles) follow-up time for all patients was 1.8 yr (0.8, 3.9). Cancer recurrence was detected in 16% (N = 40) of the no epidural therapy patients and 13% (N = 34) of the epidural therapy patients during follow-up.

Perioperative epidural analgesia was not associated with cancer recurrence ($P = 0.25$, log-rank test), with an estimated hazard ratio of 0.77 (95% CI 0.49–1.21) on univariate analysis. The Kaplan-Meier estimates of recurrence-free survival as a function of postsurgery time for the epidural therapy and the nonepidural therapy groups are provided in figure 2 and table 2; the roughly parallel shapes of the curves over time suggest no violation of the proportional hazards assumption needed for the Cox model. Table 3 details the univariate Cox regression results of relationships between cancer recurrence and available covariables.

In a multivariable model considering only the main effect of epidural use (model 1, table 4), no association between epidural use and outcome was found ($P = 0.43$), with adjusted estimated hazard ratio of 0.82 (95% CI 0.49–1.35). Sixty-one patients were excluded from the multivariable Cox regression analysis because of missing values, yielding a total of N = 448 patients.

Of the nine pairwise interaction terms assessed between the epidural use and the variables included in model 1, only the interaction with age (continuous) was statistically significant at the 0.10 level, such that the association between intraoperative epidural use and cancer recurrence depended on patient age at surgery (interaction $P = 0.01$). The interaction term seemed to be rather linear in age, based on nonsignificant higher-order age terms. For graphical display of the epidural-by-age interaction, we dichotomized age at the median of 64. No association was found for age $\leq$64 yr ($P = 0.65$), whereas better outcomes were observed for epidural use compared with nonepidural use in the older-than-64-yr age group ($P = 0.02$; figs. 3A and B). There was no evidence of violation of the proportional hazards assumption for variables in our final models as assessed by Komolgorov-type supremum tests.

Finally, the results from our sensitivity analysis, in which we adjusted for confounding through stratification on the propensity score in a Cox model, supported our aforementioned primary results. Good covariable balance between the treatment groups (all standardized differences <0.5) was observed in each propensity score quintile. In a model considering only the main effect of epidural use, no association between epidural use and colon cancer recurrence was found ($P = 0.24$), with estimated hazard ratio of 0.74 (95% CI 0.45–1.22). Moreover, we found that the epidural-by-age interaction was statistically significant ($P = 0.03$), as with the primary analysis.

Discussion

In a retrospective analysis of patients undergoing surgical treatment for breast cancer, Exadaktylos *et al.*[10] demonstrated that regional anesthesia in combination with general anesthesia was associated with a longer cancer free interval and a lower incidence of recurrence. In patients with melanoma, substitution of general anesthesia with local anesthesia was an independent favorable prognostic factor for a decrease in tumor recurrence.[19] Similar results were demonstrated in another retrospective study of patients with prostate cancer, where it was reported that open prostatectomy surgery with combined general anesthesia and epidural analgesia was associated with substantially less risk of biochemical cancer recurrence than general anesthesia with postoperative opioid analgesia.[8] Our observations stand in partial contrast to these observations, suggesting that the potential benefit of regional anesthesia on cancer recurrence may depend on the specific tumor type, which may be related to different types, mechanisms, and risk for metastasis.

Table 1. Baseline and Surgery Characteristics

Factor	Level	Miss (N)	No Epidural (N = 253)	Miss (N)	Epidural (N = 256)	*P* Value*
Baseline						
Age, yr			63 (55, 72)		65 (54, 74)	0.26
Sex	Male	1	127 (50)		156 (61)	0.02†
Ever smoker	Yes	1	106 (42)	1	116 (45)	0.49†
ASA	I		9 (4)	1	7 (3)	0.01
	II		125 (49)		162 (64)	
	III		111 (44)		76 (30)	
	IV		8 (3)		10 (4)	
Grade‡	11	30	83 (37)	38	59 (27)	0.03
	12		5 (2)		7 (3)	
	13		2 (1)		0 (0)	
	22		84 (38)		92 (42)	
	23		5 (2)		8 (4)	
	33		37 (17)		41 (19)	
	34		4 (2)		7 (3)	
	44		3 (1)		4 (2)	
Tumor stage§	0	14	3 (1)	25	1 (0)	0.09
	I		77 (32)		54 (23)	
	IIA		62 (26)		69 (30)	
	IIB		12 (5)		10 (4)	
	IIIA		12 (5)		17 (7)	
	IIIB		27 (11)		34 (15)	
	IIIC		20 (8)		24 (10)	
	IV		26 (11)		22 (10)	
T‖	T0	16	1 (0)	27	1 (0)	0.37
	T1		41 (17)		22 (10)	
	T2		42 (18)		47 (21)	
	T3		124 (52)		137 (60)	
	T4		26 (11)		21 (9)	
	T5		3 (1)		1 (0)	
N#	N0	16	159 (67)	27	138 (60)	0.13
	N1		50 (21)		58 (25)	
	N2		28 (12)		33 (14)	
M	M1-metastasis present	21	24 (10)	29	22 (10)	0.82
Surgery						
Diagnosis	Rectal cancer		74 (29)		127 (50)	<0.001†
	Colon cancer		163 (64)		120 (47)	
	Others		16 (6)		9 (4)	
Procedure**	Colectomy	2	138 (55)		99 (39)	<0.001†
Surgery procedure††	20, 26, 27, 28, 29		26 (10)		9 (4)	<0.001†
	30, 31, 32		72 (28)		118 (46)	
	40, 41		117 (46)		75 (29)	
	50, 51, 55		25 (10)		34 (13)	
	60, 65, 70, 80, 90		13 (5)		20 (8)	
Duration of surgery, min		2	160 (119, 230)	1	161 (118, 228)	0.97
EBL, ml		14	200 (100, 395)	6	262 (150, 500)	0.007
F_{IO_2} (usage %)		1	0.55 (0.5, 0.75)	2	0.54 (0.46, 0.68)	0.01
Transfusion	Yes	1	39 (15)		19 (7)	0.007†
Total Crystalloid, L			4 (2, 5)	1	4 (3, 5)	0.01
Total Colloid, ml		3	0 (0, 0)		0 (0, 0)	0.47
Temperature, °C‡‡		9	36 (36, 37)	3	36 (36, 37)	0.39
Nitrous	Yes		51 (20)		63 (25)	0.27†
Emergent	Yes		23 (9)		5 (2)	<0.001†
Chemo	Yes	30	95 (43)	25	135 (58)	0.001†
Radiation	Yes	30	50 (22)	23	89 (38)	<0.001†
Clean	Clean–contaminated	14	233 (97)	12	236 (97)	0.82†
Class of case§§	Diagnosed elsewhere		83 (33)	1	117 (46)	0.003†

(*continued*)

Table 1. Continued

Factor	Level	Miss (N)	No Epidural (N = 253)	Miss (N)	Epidural (N = 256)	*P* Value*
Infection	Yes	1	42 (17)	2	53 (21)	0.27†
Antibiotics	Yes		239 (94)		248 (97)	0.26†

Statistics are mean ± SD, median (Q1, Q3), or N (%), as appropriate.

* Wilcoxon Rank-Sum Test, unless specified. † Pearson chi-square test. ‡ Grade (rank): 11: G1, well differentiated; 12: G1/G2, tumor; 13: G1–G3, tumor; 22: G2, moderately differentiated; 23: G2/3, tumor; 33: G3, poorly differentiated; 34: G3/4, tumor; 44: G4, undifferentiated. § Tumor stage: stage 0—Tis; N0, M0; stage I—T1, N0, M0/T2, N0, M0; stage IIA—T3, N0, M0; stage IIB—T4, N0, M0; stage IIIA—T1, N1, M0/T2, N1, M0; stage IIIB—T3, N1, M0/T4, N1, M0; stage IIIC—any T, N2, M0; stage IV—any T, any N, M1. ‖ T0, no evidence of primary tumor; T1, invasion *via* submucosa into lamina; T2, invasion into the muscularis propria; T3, invasion through the subserosa; T4, invasion of surrounding structures; T5,Tis-cancer in situation (tumor present, but no invasion). # N0, no lymph nodes involved; N1, one to three nodes involved; N2, four or more nodes involved. ** Procedure: colectomy *vs*. proctorectal. †† Surgery procedure: 10, local tumor destruction; 20, local tumor excision; 26, polypectomy; 27, excisional biopsy; 28, polypectomy—endoscopic; 29, polypectomy—surgical excision; 30, partial colectomy, segmental resection; 31, wedge or segmental resection, plus resection of contiguous organs; 32, partial colectomy, segmental resection plus resection of contiguous organs; 40, subtotal colectomy/hemicolectomy; 41, subtotal colectomy/hemicolectomy plus resection of contiguous organ; 50, total colectomy; 51, total colectomy plus resection of contiguous organ; 55, total colectomy with ileostomy, not otherwise specified; 60, total proctocolectomy; 70, colectomy or coloproctotectomy with resection of contiguous organ; 90, surgery, not otherwise specified. ‡‡ First temperature in postanesthesia care unit. §§ Case diagnosed at the University of Virginia *vs*. elsewhere.

ASA = American Society of Anesthesiologists; EBL = estimated blood loss.

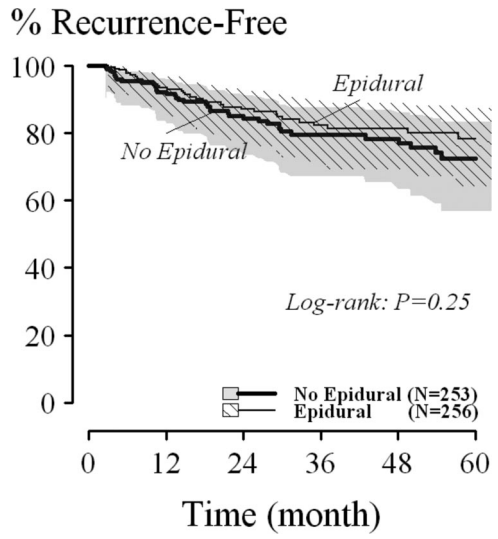

Fig. 2. Kaplan-Meier survival density function estimates, and associated 95% equal-precision confidence bands, for 256 epidural and 253 nonepidural patients (univariable $P = 0.25$, log-rank test).

Our observations differ from the findings in a smaller (177 total patients) retrospective trial by Christopherson *et al.*[9] They reported that epidural use was associated with a significant improvement in survival for the first 1.7 yr, regardless of age, in patients without metastasis at the time of surgery. Our results suggest that for younger patients, epidural use seems to have no impact on the rate of cancer recurrence, whereas for older patients, a potential benefit is observed. Apart from the difference in sample size, there is no clear difference between the data of Christopherson *et al.* and the data presented here that can explain the different findings. It is possible that there are unrecorded, subtle differences in the perioperative management of epidurals that could account for the observed differences.

The previous reports have hypothesized that the purported benefit of epidural analgesia may be related to decreased need for perioperative opioids, resulting in less opioid-induced depression of NK cell activity. NK cells are particularly important because they can spontaneously recognize and kill malignant cells, and their suppression is associated with increased rates of metastasis. Low perioperative levels of NK activity are associated with an increased cancer-related morbidity and mortality.[20] The partial blockade of

Table 2. Kaplan-Meier Survival Estimates and Equal-precision 95% Confidence Intervals

Time	Recurrence Free (%)		No. Events/No. Censored/No. Left	
	Epidural	Nonepidural	Epidural	Nonepidural
At treatment	100 (100–100)	100 (100, 100)	0/0/256	0/0/253
6 mo	98 (96–100)	95 (93–98)	5/38/213	10/53/190
1 yr	93 (90–97)	92 (88–96)	14/52/190	16/72/165
2 yr	87 (82–92)	84 (79–90)	25/105/125	28/109/115
3 yr	82 (76–88)	80 (73–86)	31/133/92	34/135/83
4 yr	82 (75–87)	78 (72–85)	32/158/66	35/158/59
5 yr	78 (71–86)	73 (64–81)	34/180/42	39/177/36
6 yr	78 (71–86)	70 (61–79)	34/198/24	40/192/20

Table 3. Univariable Associations with Cancer Recurrence: Cox Regression Model Results

Factor (Reference/Unit Increase)	*P* Value	Hazard Ratio (95% CI)*
Intraoperative epidural (no epidural)	0.26	0.77 (0.49–1.21)
Age (10 yr)	0.001	0.73 (0.61–0.87)
F_{IO_2} (10%)	0.35	0.94 (0.82–1.08)
Total crystalloid, l	0.71	1.00 (0.99–1.01)
Total colloid, ml	0.35	1.00 (1.00–1.00)
First temperature PACU, °C	0.56	1.12 (0.77–1.62)
Duration of surgery, h	0.046	1.13 (1.00–1.27)
Estimated blood loss (100 ml)	0.06	1.04 (1.00–1.08)
ASA status (per level)	0.25	1.25 (0.85–1.83)
Tumor stage (per rank)	<0.0001	1.63 (1.44–1.84)
Grade (per rank)	0.003	1.23 (1.07–1.41)
T (per rank)	<0.0001	1.89 (1.43–2.50)
N (per rank)	<0.0001	2.93 (2.19–3.91)
M (per rank)	<0.0001	6.24 (3.59–10.8)
Female gender (male)	0.69	1.10 (0.70–1.73)
Ever smoker (no)	0.09	1.48 (0.94–2.35)
Transfusion (no)	0.37	1.35 (0.69–2.64)
Nitrous (no)	0.18	0.68 (0.38–1.20)
Procedure (colectomy *vs.* proctorectal)	0.83	0.95 (0.60–1.51)
Emergent (no)	0.28	1.58 (0.68–3.64)
Chemotherapy (no)	<0.0001	3.18 (1.85–5.46)
Radiation therapy (no)	0.48	1.20 (0.72–2.00)
Clean (clean)	0.13	0.46 (0.17–1.26)
Case (UVA *vs.* elsewhere)	0.98	1.01 (0.62–1.62)
Infection (no)	0.052	1.68 (1.00–2.83)
Antibiotics (no)	0.98	—†
Diagnosis	0.52	
Rectal cancer *vs.* others		1.22 (0.37–4.04)
Colon cancer *vs.* others		1.56 (0.48–5.01)
Surgery procedure‡ (*vs.* 60, 65, 70, 80, and 90)	0.24	
Procedure 20, 26–29)		0.14 (0.02–1.13)
Procedure 30–32		0.63 (0.26–1.52)
Procedure 40, 41		0.63 (0.26–1.52)
Procedure 50, 51, and 55		0.99 (0.37–2.63)

* Risk of cancer recurrence per unit increase in factor. † No estimate of hazard ratio (95% confidence interval [CI]) provided because of very large proportion (96%) of "yes." ‡ Surgery procedure: 10, local tumor destruction; 20, local tumor excision; 26, polypectomy; 27, excisional biopsy; 28, polypectomy—endoscopic; 29, polypectomy—surgical excision; 30, partial colectomy, segmental resection; 31, wedge or segmental resection, plus resection of contiguous organs; 32, partial colectomy, segmental resection plus resection of contiguous organs; 40, subtotal colectomy/hemicolectomy; 41, subtotal colectomy/hemicolectomy plus resection of contiguous organ; 50, total colectomy; 51, total colectomy plus resection of contiguous organ; 55, total colectomy with ileostomy, not otherwise specified; 60, total proctocolectomy; 70, colectomy or coloproctotectomy with resection of contiguous organ; 90, surgery not otherwise specified.

ASA = American Society of Anesthesiologists; PACU = postanesthesia care unit; T, N, M = Tumor, Node, Metastasis system for colon cancer; UVA = University of Virginia.

Table 4. Multivariable Associations with Cancer Recurrence: Cox Multivariable Model 1, Main Effects Only (N = 448)

Factor (Reference)	*P* Value	Hazard Ratio (95%CI)*
Intraoperative epidural (no epidural)	0.43	0.82 (0.49–1.35)
Age (10 yr)	0.001	0.67 (0.54–0.84)
Duration of surgery, h	0.13	0.88 (0.74–1.04)
EBL (100 ml)	0.08	1.06 (0.99–1.12)
ASA status (per level)	0.016	1.68 (1.10–2.56)
Tumor stage† (per rank)	<0.0001	1.64 (1.44–1.87)
Ever smoker (no)	0.21	1.38 (0.84–2.25)

* Risk of cancer recurrence per unit increase in each factor. † Tumor stage: stage 0—Tis, N0, M0; stage I—T1, N0, M0/T2, N0, M0; stage IIA—T3, N0, M0; stage IIB—T4, N0, M0; stage IIIA—T1, N1, M0/T2, N1, M0; stage IIIB—T3, N1, M0/T4, N1, M0; stage IIIC—any T, N2, M0; stage IV—any T, any N, M1.

ASA = American Society of Anesthesiologists; CI = confidence interval; EBL = estimated blood loss.

sympathetic nervous activity by epidural local anesthetics plays an important role in modifying the distribution of lymphocyte subsets and NK cell activity.[21] Opioid-sparing effects of epidural analgesia may have additional benefits, as opioids inhibit cellular and humoral immune function in humans[22] and promote angiogenesis, which is essential for tumor growth.[4,6]

The observed benefit of epidural analgesia in older patients merits some discussion; however, we caution that the apparent benefit in the elderly may represent a type 1 statistical error, because we performed many *post hoc* interaction analyses. Nevertheless, two potential mechanisms could explain the observed benefit in older patients: differences in the patient and differences in the type of cancer. Given the importance of the patient's NK cells in fighting metastatic tumor cells noted earlier, it is possible that older patients, presumably with a comparatively diminished NK response, would potentially have a greater benefit from epidural analgesia. It is also possible that the type of colorectal cancer more common in older patients is different from that more common in younger patients. For example, young patients may have more aggressive disease with a worse prognosis than older patients or the population as a whole.[23] Although the multivariate model should account for this point, it is still possible that the epidural may simply be less effective in younger patients because they have a different type of tumor.

Our choice of primary statistical analysis was a multivariable model to adjust for confounding variables, enabling assessment of the effect of each potential confounding variable on the outcome simultaneously and of variables interacting with epidural use. A sensitivity analysis using propensity score analysis yielded similar results and the same conclusions.

Like any retrospective study, this analysis has several limitations. We cannot determine whether analgesia in the epidural group was sufficient and similarly cannot determine whether the epidural infusion was stopped in the perioperative period (*i.e.*, for hypotension or motor blockade). More

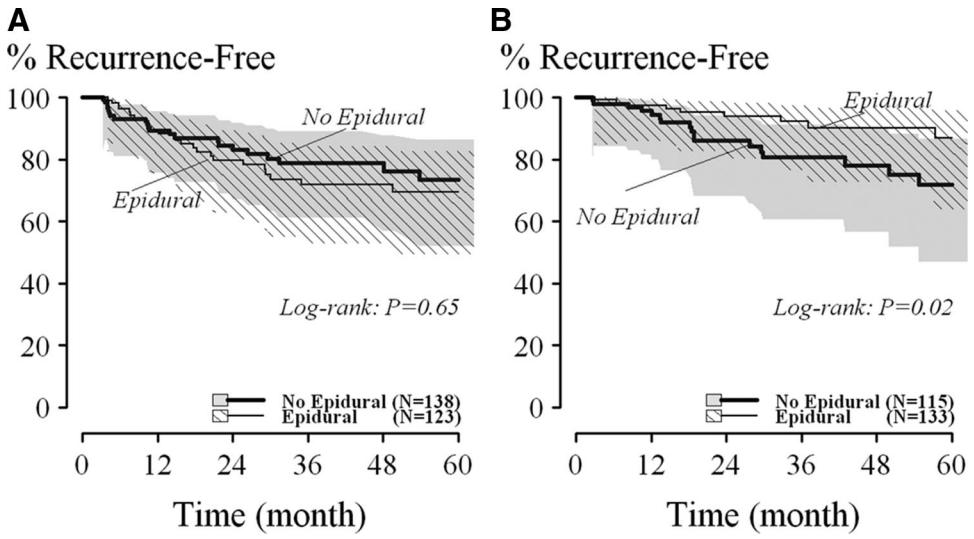

Fig. 3. Epidural use and age interaction (age categories). Kaplan-Meier time-to-recurrence plots with 95% equal-precision confidence bands comparing epidural *versus* nonepidural use by age categories (*A*: younger age group: age up to 64 yr; *B*: older age group: age older than 64 yr). The reversing of the relationship of interest for the two age groups suggests an interaction between epidural use and age.

importantly, unrecorded patient characteristics that influenced the risk of cancer recurrence may have influenced anesthetic management. Finally, the data analyzed in this study represent a relatively short median follow-up period of 1.8 yr (0.8, 3.9) yr. Given that patients with epidural analgesia had a lower reported incidence of recurrence (13%) even at this time point, compared with 16% among patients without epidural analgesia, it is conceivable that longer follow-up time may have shown greater differences. Nevertheless, Christopherson *et al.*[9] reported a benefit after a median follow-up of only 1.7 yr. Only randomized trials will fully address the relationship between regional analgesia and cancer recurrence.

Conclusions

In contrast to results from previous retrospective studies in colon, breast, and prostate surgery, we found that the use of epidural analgesia for perioperative analgesia during and after colorectal cancer surgery was not associated with cancer recurrence after adjusting for confounding variables; however, a potential benefit was observed in older patients. Our findings suggest that the benefit of regional anesthesia on cancer recurrence, to the extent that it exists, may depend critically on the specific tumor type.

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