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Review Article

The influence of anesthetic techniques on long-terms survival of colorectal cancer patients undergoing surgery: a meta-analysis

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Abstract: Background: In colorectal cancer patients undergoing surgery, some previous studies reported that perioperative epidural anesthesia is associated with better postoperative pain relief and lower incidence of additional immunosuppressive anesthetics compared with general anesthesia. There is growing evidence show that the type of anesthesia during and after cancer surgery may affect following cancer metastasis and patient survival. In this study, we tried to evaluate the influence of epidural anesthesia on survival of colorectal cancer patients undergoing surgery by performing a meta-analysis. Methods: Both retrospective and prospective studies compared the survival outcomes in colorectal cancer patients received either epidural anesthesia perioperatively or without epidural anesthesia were searched in PubMed, ClinicalTrials. gov and Web of Science. The HR of overall survival (OS) and recurrence free survival (RFS) were pooled and compared. Results: Patients received epidural anesthesia had better OS (HR: 0.75, 95% CI: 0.63-0.91, P=0.003, I^2=59%) than the counterparts without administration of epidural anesthesia. However, no significant benefits was observed in epidural anesthesia group in terms of RFS (HR: 1.04, 95% CI: 0.96-1.14, P=0.35, I^2=12%). The results of sensitive test showed that these findings are robust. Conclusion: Epidural anesthesia was associated with better OS after colorectal cancer surgery compared with the anesthetic technique without epidural anesthesia. But no benefit was observed in RFS.

Keywords: Epidural anesthesia, survival, colorectal cancer, meta-analysis

Introduction

In patients with colorectal cancer and received resection, approximately 8-25% cases had recurrence after the resection [1]. In tumor development, tumor's ability to avoid immune surveillance and to relocate directly determines whether local recurrence or metastasis occurs. Surgical manipulation might lead to release of cancer cells into the bloodstream and lymphatic vessels, causing local recurrence and metastasis [2]. Therefore, immune surveillance plays a critical role to minimize tumor cell spread during and after surgery. Previous studies observed that different anesthetic techniques had different influence on immune response and tumor behaviors. Although the use of opioids in surgery contributed to decrease mortality, its immunodeficiency effect is associated with higher cancer recurrence rate [3, 4]. Preoperative and postoperative use of opioids may inhibit cellular and humoral immune function in human [4]. Surgical stress and general anesthesia may suppress immunity through suppressing natural killer and cytotoxic T cells and also activating sympathetic nervous system [5]. However, regional anesthesia can reduce the neuroendocrine stress by blocking sympathetic nervous system, increase natural killer cell function and decrease the release of endogenous opioids [6, 7]. Therefore, epidural anesthesia combined with or without general anesthesia, had lower suppression to immune function than opioid analgesia [8]. In animal model tests, regional anesthesia was associated with reduced surgical stress response by preserving immune function and thus contributed to better post-

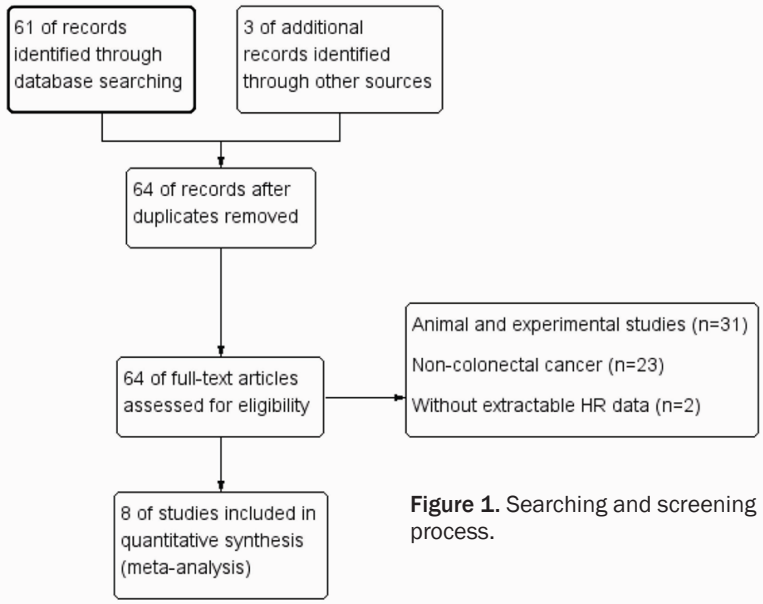

Figure 1. Searching and screening process.

operation outcomes [9]. Therefore, compared with general anesthesia, epidural anesthesia might be a better anesthetic technique for the cancer patients undergoing surgery [8].

Some clinical studies reported consistent findings with the theoretical hypothesis that regional anesthesia was associated with better post-operative outcomes of colorectal cancer surgery [10, 11]. However, some studies reported conflicting results [12, 13]. Therefore, this study aims to find out available evidence to assess the association between epidural anesthesia and post-operative survival outcomes in terms of overall survival (OS) and recurrence free survival (RFS).

Methods

Search strategy and inclusion strategy

Relevant studies were searched in the PubMed, ClinicalTrials. gov and Web of Science databases from Jan 1980 to Jan 2016 by using the following terms and strategy: ("regional anesthesia" or "epidural anesthesia") and ("metastasis" or "recurrence" or "survival") and ("colon" or "colonic" or "Rectal" or "colorectal") and ("cancer" or "carcinoma"). No language restriction was set when searching. Introduction and reference lists of included studies, relevant reviews and meta-analysis were manually searched to avoid missing of eligible studies. Studies met the criteria below simultaneously were included in this meta-analysis: (1) independent prospective or retrospective study; (2) compared the association of epidural anesthesia vs. anesthetic technique without epidural anesthesia with OS or RFS in colorectal cancer patients after surgery; (3) data of hazard ratio (HR) with 95% confidence intervals (CI) could be extracted from original studies. When available, HR adjusted for confounding or prognostic factors was extracted since it provides more accurate and reliable reflection of different anesthetic technique's real effects. Quality of included studies was assessed with The Newcastle-Ottawa Scale for assessing the quality of non-randomized studies.

Data extraction

Two authors (QG and MQ) independently performed data extraction from original studies. Discrepancy was resolved by group discussion with a third author (BW). Information extracted include first author, year of publication, cancer type, study design, number of patients in with EA and without EA group, HR with 95% CI of OS and RFS.

Statistical analyses

Cochrane Review Manager (version 5.2, Cochrane Collaboration, Copenhagen, Denmark) was used for all statistical analysis in this study. To assess the association between different anesthesia methods and post-operative survival outcomes, hazard ratio (HR) and the corresponding 95% confidence intervals (CI) of overall survival and recurrence free survival was extracted from original studies. The HR results were pooled by using inverse variance weighted method. The heterogeneity among studies was assessed by χ^2 Cochran Q tests and I^2 statistics. Fixed effects model was applied first to test heterogeneity. If I^2>50% or P<0.1, random effects model would be applied. P<0.05 was considered as significant in the Z test of pooled results. The potential publication bias was examined visually in a fun-

Table 1. The key information of studies included

Study	Cancer	Study design	Post-operative outcome	Without EA	With EA	HR	95% CI	Study quality
Christopherson 2008-I	Non-metastatic colon cancer	Prospective	Overall survival	51	61	0.216	0.065-0.718	7
Christopherson 2008-II	Metastatic colon cancer	Prospective	Overall survival	41	24	0.699	0.395-1.236	7
Gupta 2011-I*	Colon cancer	Retrospective	Overall survival	360		0.82	0.30-2.19	6
Gupta 2011-II*	Rectal cancer	Retrospective	Overall survival	295		0.45	0.22-0.90	6
Cummings 2012	Colon cancer	Retrospective	Overall survival	32,481	9,670	0.91	0.87-0.94	8
Holler 2013	Colorectal cancer	Retrospective	Overall survival	307	442	0.73	0.56-0.95	6
Vogelaar 2015	Colon cancer	Retrospective	Overall survival	189	399	0.769	0.629-0.952	7
Luo 2010	Colon cancer	Retrospective	Recurrence free survival	931	182	1.326	0.940-1.871	6
Myles 2011	Colon cancer	Prospective	Recurrence free survival	216	230	0.95	0.76-1.17	7
Gottschalk 2012	Colorectal cancer	Retrospective	Recurrence free survival	253	256	0.82	0.49-1.35	7
Cummings 2012	Colon cancer	Retrospective	Recurrence free survival	32,481	9,670	1.05	0.95-1.15	8

EA: epidural anesthesia; HR: hazard ratio; CI: confidence interval; *only reported total number of participants.

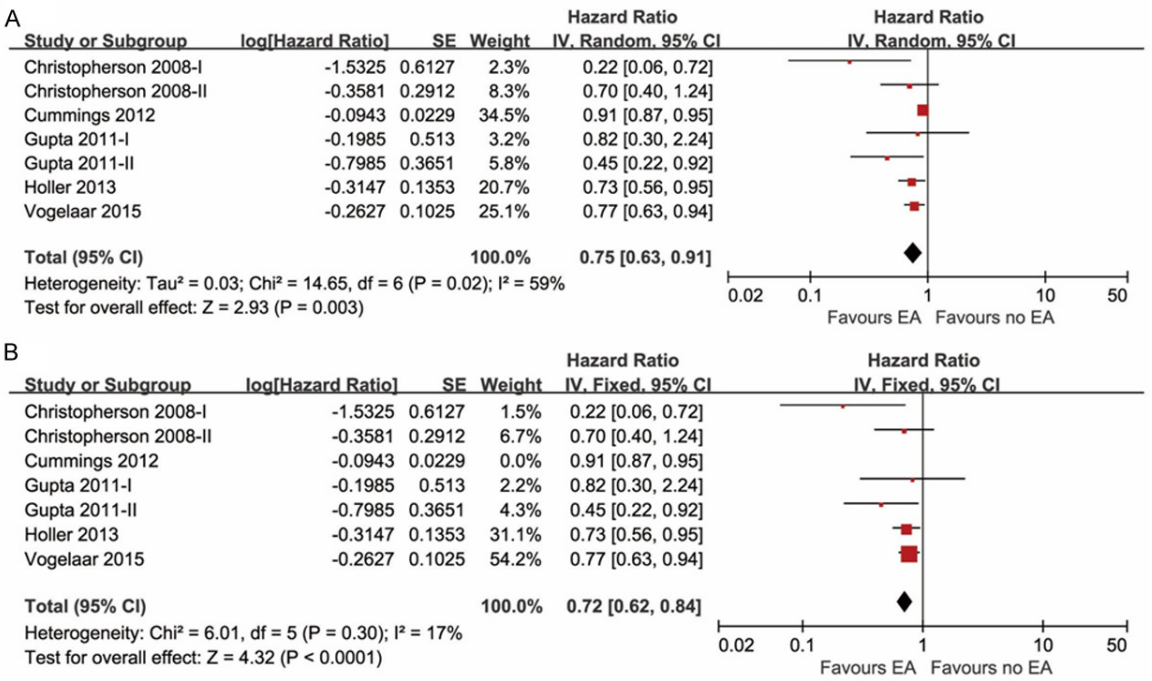

Figure 2. Meta-analysis of the association between epidural anesthesia and OS. A. Meta-analysis of the association between epidural anesthesia and OS based on five studies included; B. Meta-analysis excluding Cummings et al.'s study.

nel plot. Sensitive analysis was performed by omitting each study to assess the influence on stability of pooled outcomes.

Results

Basic characteristics of studies included

The search and screening process was described in **Figure 1**. A total of eight studies consisting 46,388 patients were finally included in this meta-analysis. The key information of the eligible studies was summarized in **Table 1**. Among them, five studies [10, 12-15] assessed the association between different anesthetic techniques and OS and four studies assessed the association with RFS [11, 12, 16, 17]. Only two studies are prospective [10, 17], while the rest six are all retrospective studies. OS was defined as the period from surgery to the death from any cause, while RFS was defined as the period from surgery to the first recurrence of tumor.

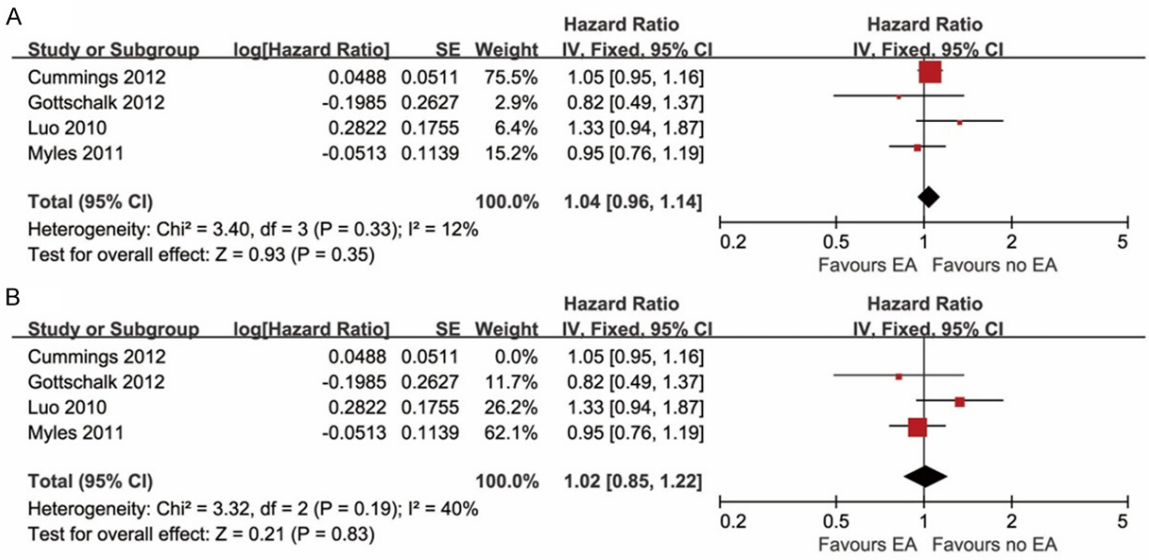

Figure 3. Meta-analysis of the association between epidural anesthesia and RFS. A. Meta-analysis of the association between epidural anesthesia and RFS based on five studies included; B. Meta-analysis excluding Cummings et al.'s study.

Association between epidural anesthesia and OS

Epidural anesthesia group had significantly better OS than the group without epidural anesthesia (HR: 0.75, 95% CI: 0.63-0.91, P=0.003) (**Figure 2A**). However, significant heterogeneity between study was observed (I^2=59%) (**Figure 2A**). Exclusion of Cummings's study (with the largest sample size that might dominate pooled results) could significantly reduce heterogeneity, and the significant association between epidural anesthesia and better OS is unchanged (HR: 0.72, 95% CI: 0.62-0.84, P<0.0001, I^2=17%) (**Figure 2B**). Exclusion of any other study could not change the robustness of the result.

Association between epidural anesthesia and RFS

Pooled result did not found significant association between epidural anesthesia and prolonged RFS (HR: 1.04, 95% CI: 0.96-1.14, P=0.35, I^2=12%) (**Figure 3A**). Since no significant between-study heterogeneity was observed, fixed model was applied to make estimate. Exclusion of Cummings's study (with the largest sample size that might dominate pooled results) did not change the trend of results (HR: 1.02, 95% CI: 0.85-1.22, P=0.83, I^2=40%) (**Figure 3B**). Similar results were obtained by excluding any of other three studies.

Assessment of publication bias

Publication bias was assessed based on OS outcome. The roughly symmetrical distribution pattern suggested there is no significant publication bias (**Figure 4**).

Discussion

Results of this meta-analysis showed epidural anesthesia was associated with better OS after colorectal cancer surgery compared with anesthetic technique without epidural anesthesia. But no benefit was observed in RFS.

Since immune surveillance is a critical determinant of cancer progression, it is reasonable to hypothesize that anesthesia techniques with less immunosuppressive effects are more beneficial to improve post-operative outcomes for cancer patients. However, this study failed to demonstrate the benefit of recurrence free survival due to use of epidural anesthesia. Therefore, probably the OS benefit is not strongly linked to better cancer control. However, compared with general anesthesia without epidural anesthesia, perioperative epidural anesthesia has less immune suppression effect, as well as better stress response, respiratory recovery, pain management and hemodynami-

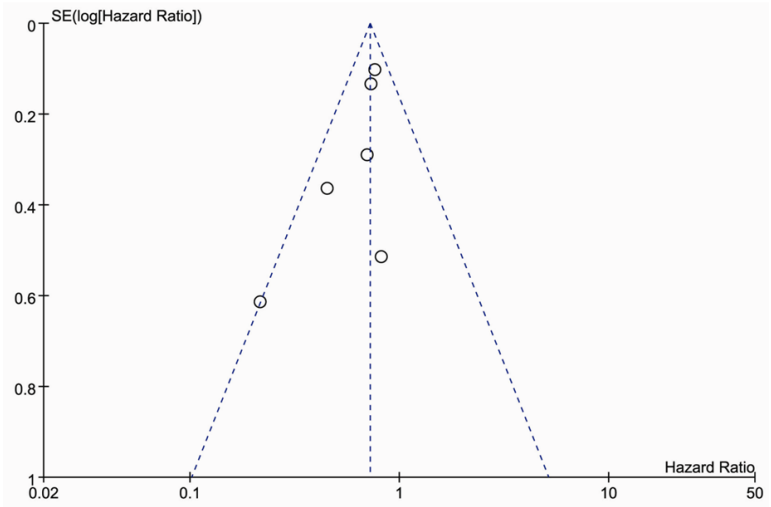

Figure 4. Funnel plot analysis of overall survival.

cal regulation that may contribute to less serious complications both during surgery and in the postoperative period [12]. This helps to explain the association between epidural anesthesia and OS benefit observed in this study. For example, Although Cummings et al.'s study did not found significant link between epidural anesthesia and RFS, they observed significantly lowered all-cause of mortality after colorectal cancer resection in epidural group than in traditional anesthesia group [12], which suggested less serious complications were associated with epidural anesthesia.

There are some other retrospective studies conducted to explore the effect of regional analgesia on disease recurrence and survival in different cancers. In patients had abdominal surgery, Myles et al.'s post-hoc analysis based on 503 patients found similar recurrence free survival in both epidural and control groups (HR: 0.95, 95% CO: 0.76 to 1.17; P=0.61) [17]. Binzack et al.' s retrospective study found a longer RFS and better OS in epidural anesthesia group than the group had combined general anesthesia and continuous subcutaneous morphine [18]. But the difference was not significant (P=0.10 and 0.16 respectively) [18]. In ovarian cancer, conflicting results were also observed. Two studies reported that benefits associated with intraoperative use of epidural anesthesia compared with general anesthesia [19, 20], while other two studies did not found significant better RFS or OS compared with non-epidural analgesia [21, 22]. In prostate cancer, previous retrospective studies also reported conflicting results. Biki et al. reported the combined general and epidural anesthesia group had 57% lower risk of recurrence compared with the general anesthesia group [8]. Wuethrich et al. reported significant longer progression free survival (HR: 0.45, 95% CI: 0.27-0.75, P=0.002) in the combined general and epidural anesthesia group compared with the general anesthesia group, but no significant difference was observed in OS and cancer specific survival [23]. Forget et al.'s study based on 1,111 patients did not found significant difference in biochemical relapse-free survival between different anesthetic groups [24]. Tsui et al.'s a secondary analysis based on patients had radical prostatectomy (50 general anesthesia cases and 49 combined general and epidural anesthesia cases) found no difference in disease-free survival at a median follow-up time of 4.5 years between these two groups [25]. Therefore, current available evidence based on retrospective studies is largely conflicting. It is still difficult to estimate the actual clinical benefits of epidural analgesia on cancer recurrence outcomes after surgery. However, findings of previous studies are largely consistent in reporting the association between epidural analgesia and OS benefit in colorectal cancer patients.

This study also has several limitations. Firstly, except two prospective studies, the rest studies are nonrandomized and retrospective. One of the major problems of these retrospective studies is the complex confounding factors such as different tumor biology, the influence of neoadjuvant and adjuvant anticancer therapies and concomitant medications could not be integrated into multivariate analysis. Secondly, colon cancer and rectal cancer might have different tumor biology. This is also one of the reasons why Gupta et al.'s study found different effect of epidural anesthesia on overall survival in colon cancer and rectal cancer patients [13]. However, due to limited number of studies available and inadequate subgroup informa-

tion, it is impossible to make subgroup analysis of these two cancers.

Conclusion

Epidural anesthesia was associated with better OS after colorectal cancer surgery compared with the anesthetic technique without epidural anesthesia. But no benefit was observed in RFS.

Disclosure of conflict of interest

None.

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