Chinese Medical Journal®

Regional anesthesia and cancer recurrence in patients with late-stage cancer: a systematic review and meta-analysis

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Abstract

Background: Whether regional anesthesia may help to prevent disease recurrence in cancer patients is still controversial. The stage of cancer at the time of diagnosis is a key factor that defines prognosis and is one of the most important sources of heterogeneity for the treatment effect. We sought to update existing systematic reviews and clarify the effect of regional anesthesia on cancer recurrence in late-stage cancer patients.

Methods: Medline, Embase, and Cochrane Library were searched from inception to September 2020 to identify randomized controlled trials (RCTs) and cohort studies that assessed the effect of regional anesthesia on cancer recurrence and overall survival (OS) compared with general anesthesia. Late-stage cancer patients were primarily assessed according to the American Joint Committee on Cancer Cancer Staging Manual (eighth edition), and the combined hazard ratio (HR) from random-effects models was used to evaluate the effect of regional anesthesia.

Results: A total of three RCTs and 34 cohort studies (including 64,691 patients) were identified through the literature search for inclusion in the analysis. The risk of bias was low in the RCTs and was moderate in the observational studies. The pooled HR for recurrence-free survival (RFS) or OS did not favor regional anesthesia when data from RCTs in patients with late-stage cancer were combined (RFS, HR = 1.12, 95% confidence interval [CI]: 0.58–2.18, $P = 0.729$, $I^2 = 76\%$; OS, HR = 0.86, 95% CI: 0.63–1.18, $P = 0.345$, $I^2 = 48\%$). Findings from observational studies showed that regional anesthesia may help to prevent disease recurrence (HR = 0.87, 95% CI: 0.78–0.96, $P = 0.008$, $I^2 = 71\%$) and improve OS (HR = 0.88, 95% CI: 0.79–0.98, $P = 0.022$, $I^2 = 79\%$).

Conclusions: RCTs reveal that OS and RFS were similar between regional and general anesthesia in late-stage cancers. The selection of anesthetic methods should still be based on clinical evaluation, and changes to current practice need more support from large, well-powered, and well-designed studies.

Keywords: Regional anesthesia; General anesthesia; Cancer recurrence; Systematic review; Meta-analysis

Introduction

Cancer is the second leading cause of mortality worldwide, leading to 9.6 million deaths in 2018.[1] The extent or stage of cancer at the time of diagnosis is a key factor that defines prognosis and is a critical element in determining the appropriate treatment that is based on the experience and outcomes of groups of previous patients with similar stages.

In addition to the impacts of disease development and surgical treatment, the potential effect of anesthetic techniques on cancer recurrence has been reported in animal and *in vitro* studies in recent years.[2-4] Regulated by the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, immune responses are induced by surgery and promote tumor angiogenesis and metastasis.[5-10] Additionally, the expression of cancer metastasis-related genes is increased by volatile anesthesia, possibly contributing to the enhancement of metastatic biological behavior.[11] As the most commonly used drugs in perioperative analgesia, opioids may also increase the possibility of cancer metastasis and recurrence.[12] In contrast, regional analgesia induces systematic anti-inflammatory action, suppresses the proliferation and migration of cancer cells, and may help to prevent the metastasis of original cancer.[13]

Several previous systematic reviews have addressed this problem but did not find any significant protective effect of regional analgesia.[14-19] Many clinical and patient factors may influence the effect of regional anesthesia on cancer recurrence, leading to potential heterogeneity in different populations, which means that some patients may benefit

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001676

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Chinese Medical Journal 2021;134(20)
Received: 19-04-2021 **Edited by:** Yuan-Yuan Ji

more from regional anesthesia. In considering the potential factors contributing to the heterogeneity, the stage of cancer should be prioritized over other factors. The American Joint Committee on Cancer (AJCC) staging system functions as a patient classifier and began to drive paradigms to stratify patient management for different cancers. Over time, it became an important factor in clinical decision-making at the bedside for each patient.[20] There were also some previous commentaries that suggested focusing on patients with a late stage of cancer because they may benefit more from intra-operative interventions during cancer surgeries.[21] As non-anatomic factors, particularly molecular markers, have become more relevant in the current genomic and precision medicine era, the debate continues regarding the inclusion of prognostic (defining the outcome) and predictive factors (predicting the response to a particular therapy). The anatomic extent of the disease remains the key prognostic factor and the strongest predictor of outcome, in most diseases.

Previous systematic reviews summarized the effect of regional anesthesia or analgesia only considering the anatomic origin of cancers, while the stage of cancers was underdetermined. We thus conducted this systematic review to collect and summarize randomized controlled trials (RCTs) and cohort studies by comparing regional and general anesthesia for cancer metastasis and recurrence in patients with late-stage cancer.

Methods

This systematic review is reported in line with preferred reporting items for systematic reviews and meta-analyses[22] and assessing the methodological quality of systematic reviews 2 guidelines.[23]

Study eligibility and literature search

We conducted a systematic review and meta-analysis of studies that assessed the effect of regional anesthesia with or without general anesthesia *vs*. general anesthesia alone; or epidural analgesia *vs*. non-epidural analgesia on cancer recurrence and all-cause mortality. Eligible studies were RCTs and cohort studies that compared any general and regional anesthetic or analgesic techniques in patients with late-stage cancer and reported outcome data for recurrence-free survival (RFS) or overall survival (OS).

Potentially relevant studies were searched from inception up to April 20, 2018, in the Medline, Embase, and Cochrane Controlled Register of Trials (CENTRAL) databases and the ClinicalTrials.gov registry. The literature search was updated on September 11, 2020, to retrieve recently published studies. Searches included keywords and MeSH/EMTREE terms for anesthetic techniques and cancers in addition to filters for RCTs and cohort studies [see Supplementary Table 1 for the search details, http://links.lww.com/CM9/A715]. The bibliographies of relevant review articles were manually searched for additional qualifying studies. There was no language limitation. A *priori*, we were especially interested in patients with late-stage cancer and thus planned to separately analyze studies that evaluated patients in this group.

Screening and abstraction of data

Duplicate citations from various databases were initially removed by EndNote bibliographic software (Thomson Reuters, Toronto, ON, Canada) and thereafter manually removed. The evaluation of qualifying references was based on a detailed practice guideline; all investigators involved in the screening completed training on how to judge the eligibility of the citations before the screening. One methodologist randomly sampled 5% of the screening results from each member to check the accuracy of the screening, and any disagreements were resolved through discussion among the group members. The reasons for excluding citations were recorded.

The data were extracted by one methodologist into an Excel extraction form and checked by an anesthesiologist. The following data were extracted from each eligible study: (1) basic information of the citation (author, publication year, study design, country, registration record, and full article or conference abstract); (2) patient characteristics (age, sex, site of original tumor, proportion of patients with late-stage cancer, and surgery); (3) details of the comparison (details of the intervention and control groups, rescue intervention, background intervention, and duration of follow-up); and (4) outcome measures (hazard ratio [HR] for RFS and OS with the corresponding standard error, recurrence and mortality events, and confounding control methods).

The stage of cancer at the time of diagnosis was defined as early stage (*in situ*/local) or late-stage (regional/distant) based on the AJCC Staging Manual (eighth edition).[24] If the staging results were reported based on other staging systems (ie, the staging records in the Surveillance, Epidemiology, and End Results Program or the International Federation of Gynecology and Obstetrics staging system), they were transferred into the corresponding AJCC stage. Detailed definitions of the late stages of cancers are provided in Supplementary Table 2, http://links.lww.com/CM9/A715. All potential sources of relevant data were used to characterize the studies, including online appendices, study registry websites, and methods publications. Survival data were extracted from the survival curves using the Parmar method when numerical values were not reported.[25]

Risk of bias assessment

The risk of bias for RCTs and observational studies was assessed with the Cochrane Collaboration's tool and the Newcastle-Ottawa Scale (NOS), respectively.[26,27] The highest NOS score was 9. The assessment was completed by two investigators independently. Any disagreements were settled by discussion after consulting the original publication.

Statistical analysis

Eligible studies were pooled using random-effects models. The inverse variance method was used to determine the weight of the eligible studies, and the DerSimonian-Laird method was used to estimate between-study variance.

The results of the meta-analyses were graphically displayed using forest plots that included the study identifier (author and publication year), sample size, point estimate of the HR, and its corresponding 95% confidence interval (CI) from individual studies, combined HR with corresponding 95% CI, and heterogeneity statistics. Gupta 2011 and Cummings III 2019 included two heterogeneous groups of cancer patients and reported the outcome data separately; hence, these studies were considered to be two separate studies in our quantitative synthesis. The original HRs and their standard errors were transformed into the natural logarithm for data synthesis. As stated above, the primary analysis in this systematic review was based on the combined HR in patients with late-stage cancer, which was identified before this review was initiated and was not a *post hoc* subgroup analysis. We regarded a population as patients with late-stage cancer when the proportion of patients with late-stage disease was ≥25%.

Predefined subgroup analyses were conducted by study design, cancer site, different intervention and control comparisons (local/epidural/spinal anesthesia *vs*. general anesthesia or epidural analgesia *vs*. no epidural analgesia), follow-up duration, bias risk, and confounder adjustment methods. A *post hoc* subgroup analysis by surgical resection extension was also conducted. Subgroup analyses by other factors in addition to the above-predefined subgroup analyses were reported as *post hoc* analyses. Combined HRs for various subgroups were compared and statistically tested for interaction. No adjustment for multiple comparisons was conducted in the subgroup analysis.

Heterogeneity was assessed using the I^2 statistic to describe the variability in effect estimates that was due to heterogeneity rather than chance. No predefined I^2 value for significant heterogeneity was used because any value is arbitrary and may be misleading.[28] Publication bias was examined using a visual inspection of the funnel plot. We conducted a sensitivity analysis by including those with early stage cancer in the combined effect. All statistical analyses were conducted using R (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria, 2020, https://www.R-project.org). A two-sided P value < 0.050 was regarded as statistically significant.

Results

A total of 3849 publications were identified by the literature search, but 483 were duplicates. The remaining 3366 records were screened by title and abstract, and 178 were potentially eligible for the analysis. After checking the full texts, 37 studies including 64,491 patients with late-stage cancer were deemed eligible and included in the final analysis [Figure 1; see the Supplementary List for the full citation list of eligible studies, http://links.lww.com/CM9/A715]. Gupta 2011 and Cummings III 2019 recruited two types of cancer patients or used two different surgical procedures and reported the recurrence data separately; hence, the reported subgroup data were regarded as two studies, and a total of 39 separate studies were synthesized in the quantitative synthesis.

Three eligible studies were RCTs. The remaining 36 eligible studies were cohort studies, of which four were prospectively designed or based on a prospective registry. RFS was reported in 31 studies, and OS was reported in 30 studies. The median proportion of patients with late-stage cancer was 53.2%. The mean age was 67.5 years, and the median sample size was 327.5, ranging from 58 to 42,151. The median proportion of male patients was 61.4%.

Eleven different cancer origin sites were included, of which colorectal, gastric, esophageal, and ovary sites were included in at least five studies. Fifteen studies compared epidural anesthesia/local anesthesia/spinal anesthesia with general anesthesia, while 24 studies compared epidural analgesia with no epidural analgesia. Randomization, propensity score, multiple regression, and matching were used in three studies, 11 studies, 18 studies, and one study, respectively. All three randomized studies were follow-up analyses of original trials in which patients had been randomized for another purpose and the balance between intervention groups during the extended follow-up may have been violated. Therefore, these randomized trials used multiple regression in addition to randomization to control the confounding effect while reporting RFS. The detailed characteristics of the eligible studies are summarized in Supplementary Table 3, http://links.lww.com/CM9/A715.

The risk of bias in the three randomized studies was thought to be low. Two of the three trials reported appropriate randomization methods, and one trial specified concealed allocation. All three trials were regarded as having a low risk of bias in terms of blinding and incomplete reporting [Supplementary Figure 1, http://links.lww.com/CM9/A715]. The mean NOS score assessing the risk of bias in cohort studies was 6.0 ± 2.0. Most of the eligible cohort studies had a low risk of bias in the domains of comparability and outcome but did not clearly report the representativeness of the exposed and non-exposed groups [Supplementary Table 3, http://links.lww.com/CM9/A715]. Visual inspection of the funnel plot for asymmetry supported publication bias [Supplementary Figure 2, http://links.lww.com/CM9/A715].

In the 31 studies of patients with late-stage cancer that reported RFS, epidural anesthesia showed a slight statistically significant effect in reducing cancer recurrence (HR = 0.88, 95% CI: 0.79–0.97, $P = 0.013$, $I^2 = 70\%$) [Figure 2]. However, two randomized trials on patients with late-stage cancer did not reveal a significant protective effect for regional anesthesia (HR = 1.13, 95% CI: 0.58–2.18, $P = 0.729$, $I^2 = 76\%$).

The three RCTs in patients with late-stage cancer did not reveal that regional anesthesia significantly improved OS (HR = 0.86, 95% CI: 0.63–1.18, $P = 0.345$, $I^2 = 48\%$) [Figure 3]. However, the remaining 28 cohort studies showed that regional anesthesia could slightly improve OS (HR = 0.88, 95% CI: 0.79–0.98, $P = 0.022$, $I^2 = 79\%$).

The results from the predefined and *post hoc* subgroup analyses are shown in Table 1. There were no differences between subgroups by different anesthetic comparisons, follow-up duration, risk of bias, publication type, study

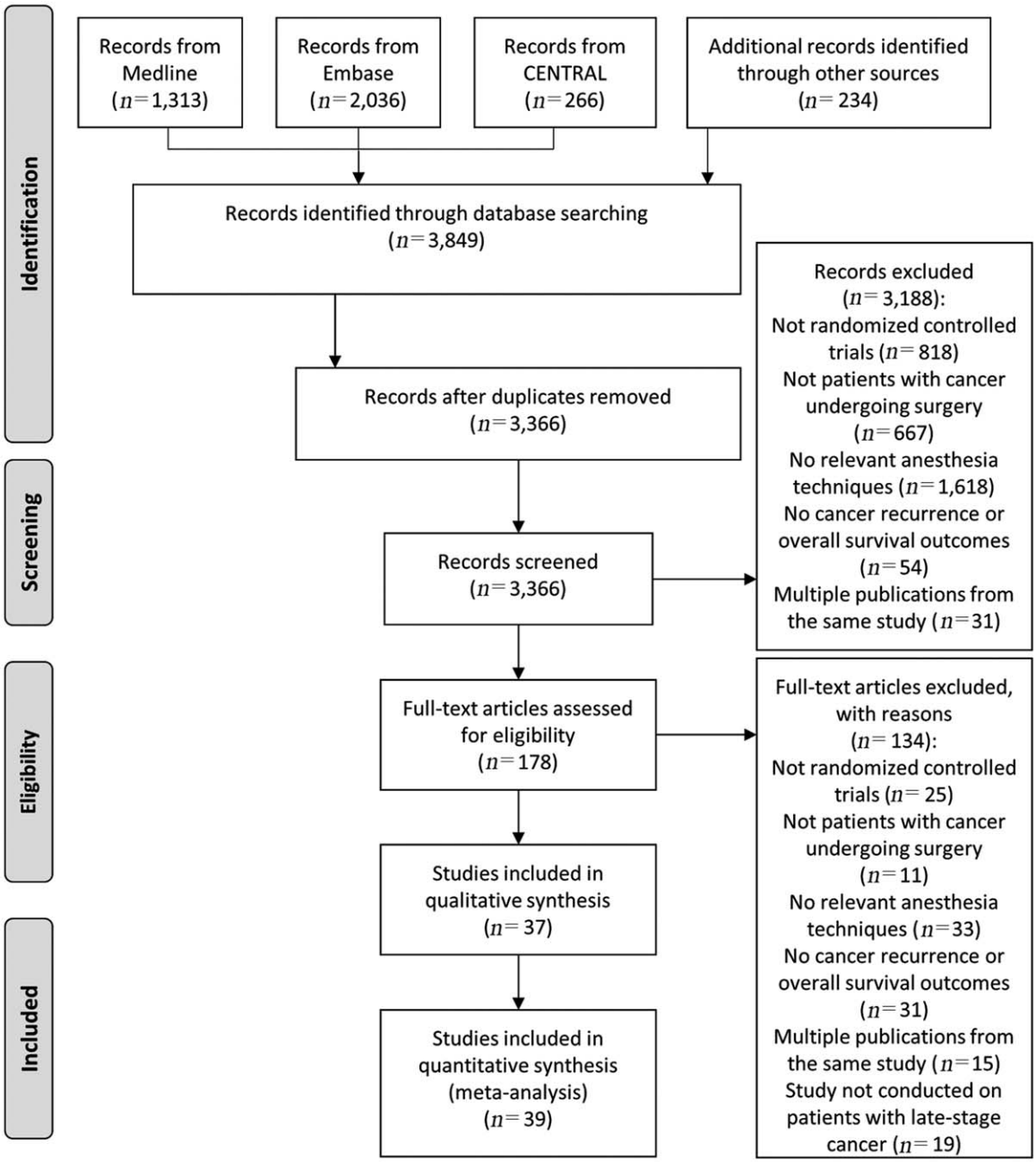

Figure 1: Literature search and screening. Gupta 2011 and Cummings III 2019 recruited two types of patients and reported the recurrence data separately; hence, they were regarded as two studies in the quantitative synthesis.

design, surgical resection extension, or original cancer site. Regional anesthesia showed a potentially larger protective effect in studies with small sample sizes and studies using propensity score as the confounding control method, but these subgroup differences cannot be explained by biological or methodological rationale. *Post hoc* subgroup analysis by surgical resection extension did not reveal any difference between patients who underwent radical surgery and those who did not (P = 0.220). None of these subgroup analyses significantly reduced the heterogeneity among the eligible studies.

In the sensitivity analysis, we included all the studies regardless of the stage of cancer and found that the pooled HR for RFS slightly favored regional anesthesia (HR = 0.89, 95% CI: 0.82–0.97, P = 0.010, I^2 = 69%, number of eligible studies = 53), and a similarly significant effect favoring regional anesthesia in terms of OS was also found (HR = 0.89, 95% CI: 0.82–0.97, P = 0.006, I^2 = 70%, number of eligible studies = 42).

Discussion

Cancer staging plays a pivotal role in the battle against cancer. First and foremost, staging provides cancer patients and their physicians the critical benchmark and standards for defining prognosis and the likelihood of overcoming cancer once diagnosed and for determining the best treatment approach to

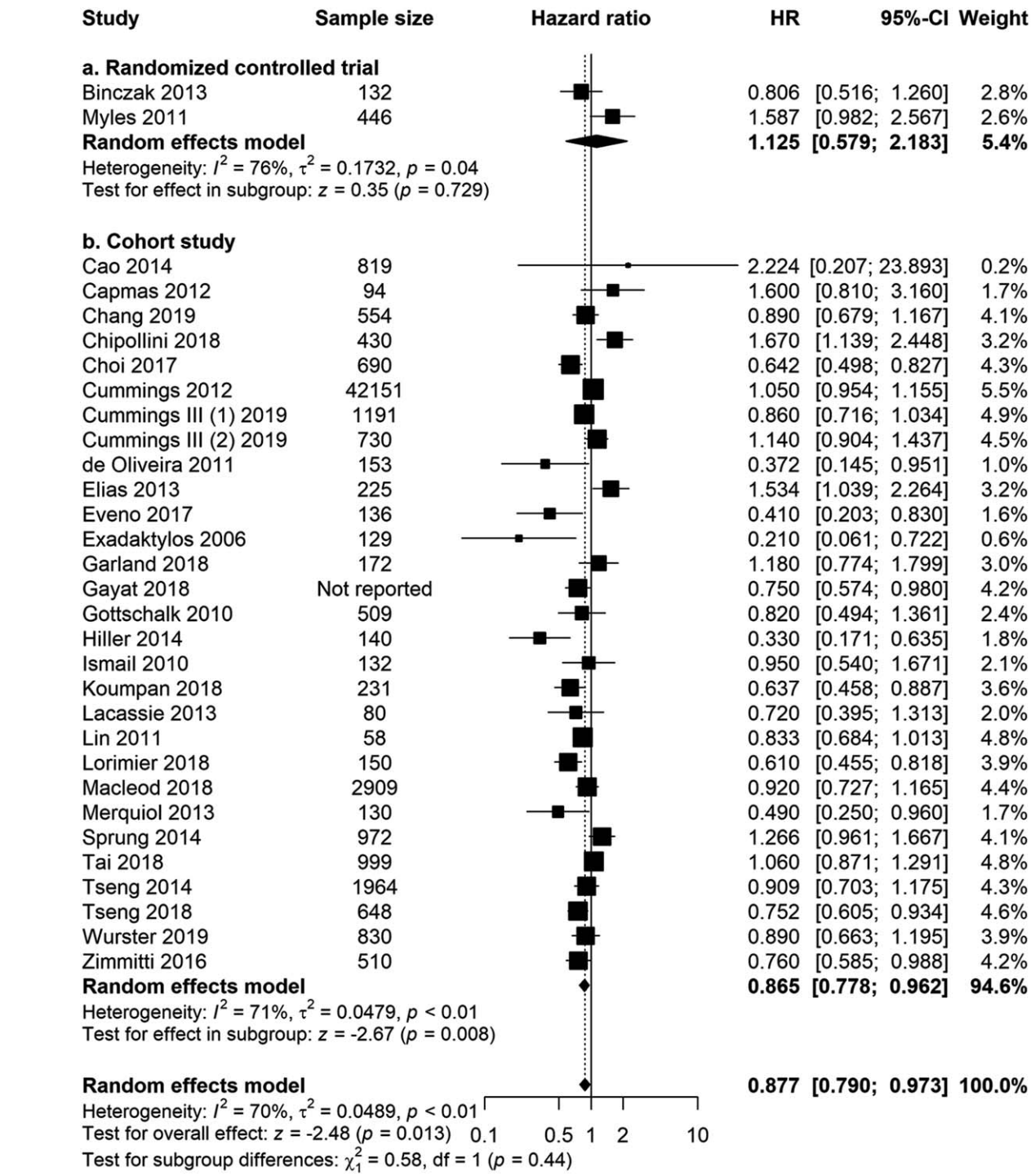

Figure 2: Meta-analysis of HRs for RFS comparing local/epidural/spinal anesthesia *vs.* general anesthesia in patients with late-stage cancer by study design. An HR value <1 indicates that local/epidural/spinal anesthesia will decrease the risk of recurrence. CI: Confidence interval; HRs: Hazard ratios; RFS: Recurrence-free survival.

manage the disease. Staging is the foremost classifier of cancer patients and defines groups for inclusion in clinical trials and analyses of outcome data in clinical studies. For clinicians and scientists engaged in research, it provides consistent nomenclature, which is essential for the study of cancer from biology to clinical presentation and management.

Our analyses implied that regional anesthesia may have a slight effect on preventing cancer recurrence and improving OS in patients with late-stage cancer. The contradictory results regarding the potentially heterogeneous effect of regional anesthesia identified in the present study compared with the absence of an effect found in previous studies that did not fully consider the stage of disease may be somewhat explained by the fact that the previous studies mainly treated the patients as a single population rather than dividing them into different subgroups.

The earliest systematic review on this topic, which was published in 2013, collected evidence from 14 studies and

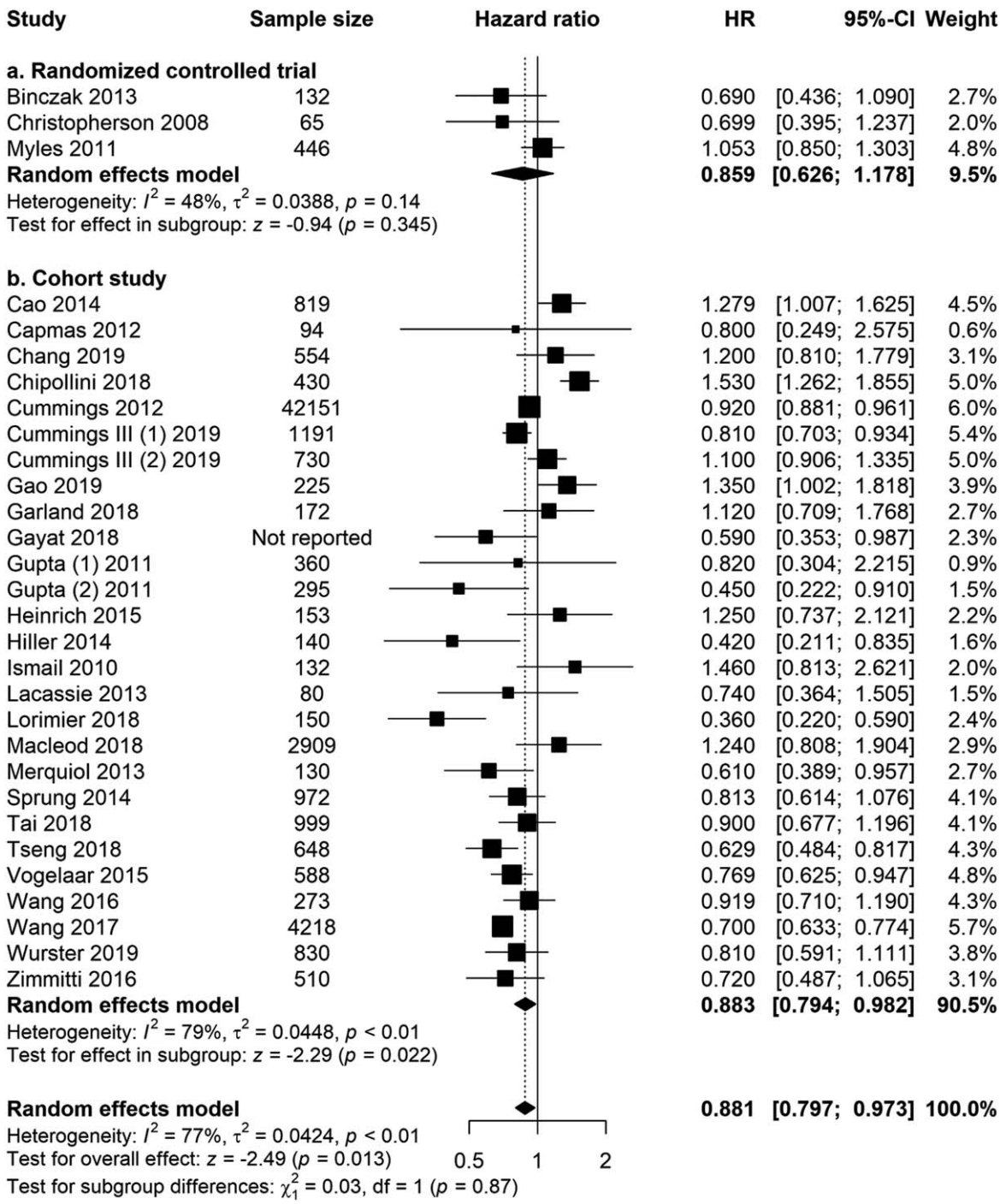

Figure 3: Meta-analysis of HRs for OS comparing local/epidural/spinal anesthesia *vs.* general anesthesia in patients with late-stage cancer by study design. An HR value <1 indicates that local/epidural/spinal anesthesia will decrease mortality. CI: Confidence interval; HRs: Hazard ratios; OS: Overall survival.

found that regional anesthesia can improve OS but not progression-free survival.[15] Following this review, one Cochrane review[14] synthesizing four RCTs, one evidence synthesis[17] in patients receiving prostatectomy, and one systematic review[18] combining ten studies did not find a beneficial effect of regional anesthesia on OS. A recently published review[19] compared volatile anesthesia and propofol-based total intravenous anesthesia in one randomized and nine retrospective studies and concluded that propofol-based total intravenous anesthesia improved RFS. Despite these existing systematic reviews, we still conducted the present review because all the existing reviews may suffer from selection bias. The maximum number of eligible studies in previous reviews was 28, compared with the 37 eligible studies (64 eligible studies if there were no exclusion criteria about the late stage of disease) in our review. We suspected that some evidence was missed during the literature search and screening in the existing reviews, most likely leading to biased combined results.

Table 1: Subgroup analysis of combined HRs for RFS comparing regional with general anesthesia in patients with late-stage cancer.

Items	Number of studies in the subgroup	HR (95% CI)	I^2 (%)	*P* for subgroup difference
Overall	31	0.88 (0.79–0.97)	70	–
Comparison				0.865
EA/LA/SA *vs.* GA	14	0.87 (0.73–1.03)	69	
EA *vs.* no EA	17	0.88 (0.77–1.01)	72	
Duration of follow-up				0.729
>5 years	5	0.87 (0.74–1.01)	22	
≤5 years	18	0.83 (0.71–0.97)	76	
Sample size				0.013
>200	18	0.96 (0.86–1.07)	69	
≤200	12	0.69 (0.54–0.87)	63	
Risk of bias				0.851
Low risk	21	0.88 (0.79–0.98)	73	
High risk	10	0.85 (0.61–1.17)	67	
Confounding adjustment				0.040
Crude	2	0.91 (0.59–1.42)	68	
Matching	1	1.27 (0.96–1.67)	–	
Multivariable regression	15	0.90 (0.77–1.04)	75	
Propensity score	11	0.78 (0.67–0.90)	46	
Randomization	2	1.12 (0.58–2.18)	76	
Publication type				0.854
Full article	27	0.87 (0.78–0.97)	70	
Conference abstract	4	0.91 (0.57–1.45)	80	
Study design				0.144
Prospective cohort study	3	1.00 (0.89–1.13)	16	
Retrospective cohort study	26	0.85 (0.75–0.96)	70	
RCT	2	1.12 (0.58–2.18)	76	
Cancer site				0.255
Abdominal cancer	2	1.12 (0.58–2.18)	76	
Carcinoma of ovary, fallopian tube, or primary peritoneal origin	6	0.91 (0.68–1.21)	70	
Carcinoma of the breast	1	0.21 (0.06–0.72)	–	
Carcinoma of the cervix uteri	1	0.95 (0.54–1.67)	–	
Colorectal cancer	7	0.90 (0.77–1.06)	66	
Hepatocellular cancer	2	0.90 (0.69–1.18)	0	
Laryngeal/hypopharyngeal cancer	1	0.49 (0.25–0.96)	–	
Multiple cancers	2	0.61 (0.35–1.07)	59	
Prostatic cancer	3	1.01 (0.82–1.24)	48	
Upper gastrointestinal, esophageal, and esophagogastric junction cancer	3	0.78 (0.51–1.20)	85	
Urinary bladder	3	0.87 (0.49–1.53)	89	
Surgical resection extension				0.219
No reported radical surgery	26	0.85 (0.76–0.95)	69	
Radical surgery	5	1.04 (0.76–1.41)	76	

A study was regarded as having a low risk of bias if the score from the NOS was >5 or if three or more domains from the Cochrane tool were evaluated as low risk of bias. CI: Confidence interval; EA/LA/SA *vs.* GA: Epidural anesthesia/local anesthesia/spinal anesthesia *vs.* general anesthesia; EA *vs.* no EA: Epidural analgesia *vs.* no epidural analgesia; HRs: Hazard ratios; NOS: Newcastle-Ottawa Scale; RCT: Randomized controlled trial; RFS: Recurrence-free survival.

In theory, the best evidence for assessing the effect of regional anesthesia on cancer recurrence should come from well-designed randomized studies. However, as summarized in our analyses, only three previous randomized studies compared regional anesthesia with general anesthesia in patients with relatively late-stage cancer, and most of these trials were severely underpowered.[29-31] All of these trials yielded a null effect for regional anesthesia. It is still unclear whether regional anesthesia is beneficial for cancer patients based on only these small trials. The large well-powered multicenter Breast Cancer Recurrence Trial comparing paravertebral blocks combined with propofol and volatile opioid anesthesia published the main findings recently but did not reveal a significant beneficial effect of regional anesthesia on breast cancer recurrence.[32-34] The low proportion of late-stage patients in this trial (18.8% had stage 3 or higher disease) may explain the null effect. In addition to the evidence from trials, we also collected evidence from 34 cohort studies. Several confounding control methods were applied in these cohorts, but it is still possible that the findings in the cohort studies suffer from residual confounding effects and other sources of bias.

We primarily focused on patients with late-stage cancer rather than the overall cancer population because the baseline recurrence and metastatic risk, which are directly reflected by the stage of disease, are the most common explanatory factors that can explain the heterogeneity of the effect due to the underlying mathematical relationship between the baseline risk and treatment effect.[20] A recently updated review[21] suggested the concept of an "early peak of recurrence in the first 18 months after breast cancer surgery." The survival curves in the Breast Cancer Recurrence Trial were not associated with any early peak of recurrence,[34] which would suggest that the course of the disease might have changed over time. Therefore, Prof. Juan P. Cata suggests that the focus of future investigations should be on patients with a higher risk of early recurrence who may benefit more from intra-operative interventions during cancer surgery. Patients with late-stage cancer may potentially have a higher risk of early recurrence. Unlike single predictors of the effect (eg, patients' age, sex, or surgery type), the baseline risk, or patients' metastatic risk of original cancer in our research context, is a good proxy for many undetermined impact factors for the treatment effect. As a highly heterogeneous disease, cancer from different anatomic origins may have very different biological behaviors. The stage of disease can not only reflect the local, lymph node, and metastatic development of the tumor but also provide an opportunity for evaluating the overall biological behaviors of the disease. Positive findings from *in vitro* and *in vivo* studies may be diluted in population-based studies due to the recruitment of patients with early stage disease. The potential effect modification by the stage of disease in our review strongly implies that future studies assessing the effect of regional anesthesia on cancer recurrence should consider primarily recruiting patients with late-stage disease.

Although we found slightly significant benefits of regional anesthesia in some subgroups, these findings should be interpreted with caution while generating hypotheses because the combined effects in the subgroups were based on a small number of original studies, and there was no correction for multiple comparisons. Given the limited and heterogeneous evidence, it may be too early to change the anesthesia practice in surgeries for cancer, but we believe our findings suggest future studies in this area.

There are some limitations to our analysis. Although 37 studies were identified after the inclusion and exclusion criteria, only three RCTs were included, and all of them recruited only a small number of patients. These three trials were regarded as randomized studies in a previous systematic review, although all were follow-up analyses of original trials in which randomization was performed for other outcomes. A consequence is that the cancer-related inclusion and exclusion criteria were not considered during enrolment. Furthermore, potentially important cancer-related information was not originally collected and not necessarily available for subsequent analysis. Considering the potential risk of bias, these trials can be considered as studies lying somewhere between traditional RCTs and cohort studies. All information about the stage of cancer was only collected from the published literature. Primarily designed for assessing the effect of regional anesthesia for breast cancer recurrence, the Breast Cancer Recurrence Trial was finally excluded from our primary analysis due to the relatively early stage of cancer of the study population. Given the negative findings from our analysis, well-designed and conducted retrospective observational studies are still warranted to evaluate the effect of regional anesthesia on cancer recurrence in patients with late-stage cancer before conducting new trials. There was substantial heterogeneity among the eligible studies, especially for the eligible cohort studies. Patients with different cancer origins were combined. Although we conducted subgroup analysis based on cancer origins, the number of studies and patients in each subgroup were too small to draw any solid conclusion. Furthermore, heterogeneity remained after the subgroup analysis. Diverse practice settings, personnel, and study designs may contribute to the heterogeneity; unfortunately, such factors are rarely reported in sufficient detail.

In conclusion, the present study showed little difference in OS and RFS between regional anesthesia and general anesthesia in late-stage cancer patients. Our results should be considered exploratory at best and certainly not a basis for changing practice. On the other hand, they strongly suggest that large, well-designed RCTs in populations with late-stage cancer are needed.

Registration Number

CRD42018096093 (https://www.crd.york.ac.uk/prospero) and reviewregistry1065 (https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/).

Acknowledgements

The authors thank Prof. Daniel I. Sessler (Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA) for his comments on this manuscript.

Funding

This study was supported by a grant of Peking Union Medical College Hospital Research Grant for Young Scholar (No. pumch201912048).

Conflicts of interest

None.

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How to cite this article: Zhang YL, Pei LJ, Sun C, Zhao MY, Che L, Huang YG. Regional anesthesia and cancer recurrence in patients with late-stage cancer: a systematic review and meta-analysis. Chin Med J 2021;134:2403–2411. doi: 10.1097/CM9.0000000000001676