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Effect of Regional Anesthesia on Oncological Outcomes (Meta-Analysis)

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Highlight. Regional anesthesia when used in combination with general anesthesia has no effect on oncological outcomes.

Summary

Metastatic processes remain the main cause of deaths in oncology. Methods of anesthesia, in particular regional anesthesia, are considered as potential modulators of the immune response and metastatic spread. The ambiguity of the available data on the effect of regional and general anesthesia on metastatic spread is partly due to the fact that general anesthetic in combined anesthesia is quite often not taken into account, and this, in turn, masks the possible influence of regional anesthesia.

The purpose of this meta-analysis was to make a comparative assessment of the effect of general anesthesia and general anesthesia in combination with regional anesthesia on the relapse-free and overall survival of cancer patients after surgery.

Materials and methods. We analyzed 8 randomized controlled trials involving 1822 patients and comparing the groups of cancer patients who were operated either under general anesthesia (total intravenous (TIVA) or inhalation (IA)), or general anesthesia in combination with regional anesthesia (TIVA+RA or IA+RA, respectively). Trial using combinations of inhaled and intravenous anesthetics was excluded from the analysis for a more accurate assessment of the effect of regional anesthesia. The study complies with the recommendations of the Cochrane Community and PRISMA standards. The protocol was registered on the INPLASY platform. We used PubMed, Google Scholar and CENTRAL databases. We used a subgroup analysis and GRADE tool to assess the quality of evidence.

Results. There were no statistically significant differences in relapse-free and overall survival when comparing different anesthesia methods. For a relapse-free survival, comparing TIVA vs TIVA+RA resulted in no significant difference: OR=1.20 [95% CI 0.92–1.55]; when IA vs IA+RA were compared, OR=1.10 [95% CI 0.94–1.29]. Similar results were obtained for overall survival.

Conclusion. Based on the meta-analysis results, regional anesthesia had no effect on relapse-free and overall survival in oncosurgery patients.

Keywords: regional anesthesia; oncological outcomes; general anesthesia; metastases; surgical

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Introduction

The increased focus on metastasis is understandable given that metastatic processes, rather than primary tumors, account for the vast majority (90%) of cancer-related mortality. Surgical stress can induce a systemic inflammatory response syndrome (SIRS), which activates the sympathetic and hypothalamic-pituitary axis and affects the progression of metastatic cancer [2]. However, in the last decade, research interest in the risk of metastasis has shifted from the traditional mechanisms of intraoperative surgical stress to the importance of perioperative immunomodulation. This factor has

become increasingly important in the assessment of tumor recurrence, highlighting the vulnerability of the perioperative period in terms of long-term outcomes in oncology [3]. Even in the early stages of tumor development, circulating tumor cells are present in various parts of the body [4], and although they are associated with a poor clinical prognosis [5], less than 0.01% of these cells develop into metastatic foci [6]. The discovery that anesthetics can modulate receptor targets on immune cells supports the hypothesis that anesthetic agents have a significant effect on long-term outcome in cancer [7, 8]. Several studies have confirmed this pattern by demonstrating that some anesthetics have a negative effect on the functional activity of natural killer cells, macrophages, and neutrophils [9, 10]. The emphasis on accelerated recovery after surgery (ERAS) protocols, which include anesthesia and post-anesthesia rehabilitation techniques, has resulted in the extraordinary popularity of regional anesthesia techniques or neuroaxial blocks due to improved postoperative pain control, reduced opioid consumption, and shorter hospital stays [11, 12]. However, during the last decade, several randomized clinical trials have been performed to test hypotheses about the effect of regional anesthesia on the metastatic potential of malignant tumors, and their results, including those included in meta-analyses, have not shown significant advantages of regional anesthesia over general anesthesia in terms of overall and recurrence-free survival [13, 14]. However, it should be noted that the comparison of mixed groups with different types of general anesthesia may have a significant impact on the final results.

The aim of this meta-analysis was to compare the effects of general anesthesia and a combination of general and regional anesthesia on recurrence-free and overall survival in cancer patients after surgical intervention.

Materials and Methods

The study was conducted according to the guidelines of the Cochrane Society and met the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards for systematic reviews and meta-analyses [15]. The study protocol was registered on the International Platform for Systematic Reviews and Meta-Analyses Protocols (INPLASY) under registration number INPLASY202390088 (doi:10.37766/inplasy2023.9.0088).

Search strategy. A systematic search of PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for scientific articles published between 2008 and 2023 was performed by two independent investigators. Searches were conducted in the form of queries: («anesthesia, inhalation»[MeSH] OR «anesthesia, intravenous»[MeSH] OR «anesthesia, general»[MeSH] OR «anesthesia, conduction»[MeSH] OR sevoflurane OR isoflurane OR propofol OR midazolam OR «anesthesia, regional» OR «anesthesia, epidural» OR «epidural analgesia» OR «anesthesia, mixed» OR «paravertebral block») AND («neoplasms» [MeSH] OR «cancer» OR «carcinoma» OR «neoplasm» OR «malignancy» OR «tumor» OR «NSCLC») AND («survival»[MeSH] OR «survival analysis»[mesh] OR «survival rate»[MeSH] OR «disease-free survival» OR «recurrence-free survival» OR «event-free survival» OR «overall survival» OR «recurrence-free survival»). In addition, the sources in the reference list of previously identified articles were analyzed (backward snowballing) and citations were analyzed (forward snowballing). No language restrictions were applied. MeSH (Medical Subject Headings) terms were used.

Study selection. We independently screened the studies extracted from the databases at the title and abstract analysis stage. We reviewed randomized controlled trials (RCTs) comparing groups of cancer patients who received total intravenous or inhalation anesthesia (TIVA or IA) versus general anesthesia combined with regional anesthesia (TIVA+RA or IA+RA) during surgery. Comparisons were made for recurrence-free and overall survival. After duplicate records were excluded, the final decision to include articles was based on a detailed analysis of the full-text articles by two independent reviewers. Disagreements were resolved by consensus.

The following inclusion criteria were used:

1) RCTs comparing the use of general anesthesia and regional anesthesia in combination with general anesthesia in adult patients undergoing cancer surgery;

2) the study reported recurrence-free and/or overall survival of patients.

Studies were excluded if they met at least one of the following criteria:

1) cross-comparisons (TIVA vs. IA+RA, IA vs. TIVA+RA) and other anesthesia protocols;
2) no data on survival outcomes;
3) observational or retrospective studies;
4) clinical observational studies;
5) reviews;
6) meta-analyses;
7) pediatric patients.

Data retrieval and outcome measurements. Basic study information (first author, design, sample size, type of anesthesia, patient enrollment period, inclusion criteria, patient follow-up period), subject information (age, proportion of males, TNM stage, ASA scale, tumor type, surgical procedure, and duration), and treatment outcomes were retrieved independently by two investigators and then compared for validation. The study endpoints were overall survival (OS) and relapse-free survival (RFS) at 1, 2, 3, and 5 years from diagnosis. Kaplan-Meier curve analysis, as described in the original papers [16], was used to retrieve survival data when necessary.

Assessment of risk of bias. The internal validity and risk of systematic error (bias) of the included studies were assessed by two independent reviewers using the latest version of the Cochrane Risk-of-Bias Tool 2.0 (RoB 2) [17]. Discrepancies in estimates were resolved by consensus. Systematic publication error or «publication bias», which results from a bias towards publishing studies with statistically significant results, was assessed using the Egger test and analysis of funnel plots [18].

Statistical analysis. STATA 17 (StataCorp LLC, Texas, USA) was used to perform the meta-analysis. Heterogeneity between studies was assessed using Cochran's Q criterion and I^2 heterogeneity coefficient. Significant heterogeneity was defined as $P<0.05$ and/or $I^2 \geqslant 50\%$. The odds ratio (OR) and corresponding 95% confidence interval for OS and RFS were calculated for each individual study using the inverse variance (Mantel-Haenszel) method [19]. The recommended random effects model (REML, or restricted maximum likelihood) [20] was used to pool the results and calculate an overall OR. The statistical significance (*P* value) for hypothesis testing was set at 0.05.

Subgroup analysis. Subgroup analyses were performed using several methodological approaches.

First, separate comparisons were made for two categories of studies: TIVA versus a combination of TIVA and RA (TIVA+RA), and IA versus a combination of IA and RA (IA+RA).

Second, a sequential exclusion method was used to assess the robustness of the results, in which each study was removed from the overall analysis and then reanalyzed.

In addition, separate analyses of survival at 1, 2, 3, and 5 years were performed.

Quality of evidence assessment. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) systematic approach [21] was used to assess the quality of evidence for all outcomes studied. According to current guidelines, the baseline level of evidence for RCTs is considered high [21]. Two authors of this review independently assessed the quality of the evidence, and disagreements were resolved by consensus.

Results and Discussion

The primary search identified 1695 articles, of which 85 full-text articles were analyzed according to the inclusion and exclusion criteria. A flowchart illustrating the study selection process is shown in Fig. 1.

A total of 1822 patients from 8 RCTs were included in the meta-analysis [22–29].

Three of the eight included studies compared TIVA versus TIVA+RA [22–24] and five compared IA versus IA+RA [25–29]. Two studies included patients with breast cancer [23, 24], while other studies included patients with colorectal cancer, non-small cell lung cancer, and prostate cancer (Table 2). Two studies used double blinding [24, 28], four studies used single blinding [22, 23, 26, 27], and two studies used no blinding [25, 29]. Two studies used propofol for induction in the IA group [25, 27]. The proportion of patients with metastatic lesions at the time of diagnosis ranged from 0 to 23%, and the mean age of patients ranged from 51 to 70 years (Table 1). The characteristics of the included studies are summarized in Table 1.

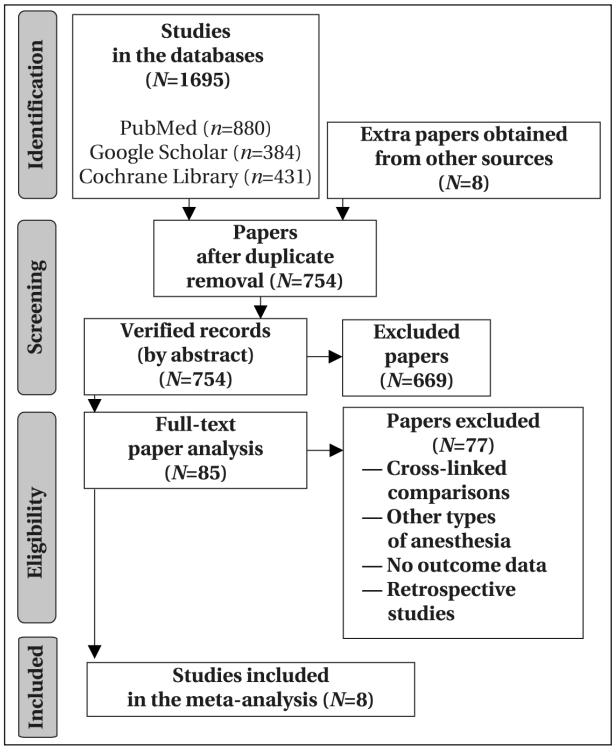

Fig. 1. Flowchart of the meta-analysis.

Recurrence-free survival. Fig. 2, a is a forest plot illustrating the results of a meta-analysis of three studies involving 819 cancer patients. These studies compared RFS with two different anesthetic techniques, TIVA and combined TIVA+RA. According to the meta-analysis, no significant differences were found between the two groups with OR=1.20 [95% CI 0.92–1.55], *P*-value for effect 0.17, *P*-value for heterogeneity 0.74, I^2=0% (Fig. 2, *a*; Table 2).

A meta-analysis reviewed data from four studies involving 826 cancer patients. These studies compared RFS using two methods of anesthesia, IA versus IA+RA. No significant differences were found with OR=1.10 [95% CI 0.94–1.29], *P*-value for effect 0.24, *P*-value for heterogeneity 0.22, I^2=0% (Fig. 2, *b*; Table 2).

Overall survival. Fig. 2, *c* shows a forest plot illustrating the results of a meta-analysis of two studies (676 patients) comparing OS of TIVA and combined TIVA+RA. No significant differences were found between the two groups with OR=1.09 [95% CI 0.70–1.70], *P*-value for effect 0.70, *P*-value for heterogeneity 0.68, I^2=0% (Fig. 2, *c*; Table 2).

Table 1. Characteristics of RCTs included in the meta-analysis.

Ref No.	Author, year of publication, country, journal	Blinding	Number of centers	Methods compared	Sample size, GA/GA+RA	Mean age, years	Percentage of men, %	BMI, kg/m²	Cancer type	Surgery	Duration of surgery, min
29	*Christopherson R.*, 2008, USA, *Anesth Analg*	No	Multicenter	IA/IA+RA	177.92/85	68.85	100	26.5	CRC	Colon resection	NA
28	*Binczak M.*, 2013, France, *Annales Ann Fr Anesth Reanim*	Double	Single-center	IA/IA+RA	132.63/69	57.5	62.9	НД	Various	Abdominal surgery	NA
27	*Tsui B. C.*, 2010, Canada, *Can J Anesth*	Single	Single-center	IA/IA+RA	99.50/49	63.45	100	28.15	Prostatic adenocarcinoma	Prostatectomy	114.5
26	*Myles P. S.*, 2011, Australia, New Zealand and other, *BMJ*	Single	Multicenter	IA/IA+RA	446.216/230	70.5	56.5	НД	Various	Abdominal surgery	NA
25	*Pi J.*, China, *J Int Med Res*	No	Single-center	IA/IA+RA	149.75/74	51	51.7	22.7	NSCLC	Resection	218.37
24	*Karmakar M. K.*, 2017, China, *Anticancer Res*	Double	Single-center	TIVA/TIVA+RA	173.58/115	51.3	0	НД	BC	Mastectomy	NA
23	*Yu L.*, 2022, China, *BMC Surgery*	Single	Single-center	TIVA/TIVA+RA	503.252/251	52.15	0	23.90	BC	Mastectomy	83.5
22	*Rangel F. P.*, 2021, Brasil, *BMJ*	Single	Single-center	TIVA/TIVA+RA	143.71/72	67	100	24.10	PC	Prostatectomy	NA

Note. GA — general anesthesia; RA — regional anesthesia; TIVA — total intravenous anesthesia; IA — inhalation anesthesia; BMI — body mass index; CRC — colorectal cancer; NSCLC — non-small cell lung cancer; BC — breast cancer; PC — prostate cancer; NA — not available.

An analysis of four studies (904 patients) comparing the OR for IA versus IA+RA showed no significant differences with OR=1.22 [95% CI 0.97–1.53], *P*-value for effect 0.09, *P*-value for heterogeneity 0.37, I^2=19% (Fig. 2, *d*; Table 2).

The lack of statistically significant differences was confirmed in all subgroup analyses, including survival at different time periods.

The assessment of study quality showed that only one study was at high risk of bias (Fig. 3).

The risk of systematic publication bias was significant for the comparison of IA vs. IA+RA in the assessment of OS (*P*=0.003), as confirmed by funnel plot analysis (Fig. 4).

The quality of evidence for the outcomes reviewed was assessed using the GRADE methodology. Factors that led to a downgrading of the level of evidence are summarized and shown in Table 3. The level of evidence for RFS and OS ranged from very low to low.

This meta-analysis was the first to evaluate the long-term outcomes of cancer patients in the context of the use of regional and general anesthesia, taking into account the differentiation of general anesthesia groups into inhalation and intravenous anesthesia groups.

Despite the high methodological reliability of the included studies, the level of evidence for recurrence-free survival and overall survival ranged from very low to low. Nevertheless, the study supports previous findings that regional anesthesia has no significant advantages over total intravenous and inhalation anesthesia in the context of long-term oncologic outcomes. The results are comparable to the conclusions of previous meta-analyses, which had an unfavorable balance between randomized clinical trials and retrospective studies [30–32]. In the largest meta-analysis, which included 25 retrospective studies and 3 randomized clinical trials with a total of 67577 patients, although there was no significant overall survival benefit when the averaged data were analyzed, a small survival benefit was found when only RCTs were considered, with weighted hazard ratios of 0.83 (HR=0.83) and 0.88 (HR=0.88) for overall and recurrence-free survival, respectively [31].

Traditional concepts of malignant recurrence and progression suggest that immune function plays a key role in tumor cell survival [33, 34]. In this context, studies have investigated the relationship between analgesics and tumor progression. For example, mu-opioid receptor agonists stimulate tumor cell migration, growth, and metastasis [35]. In contrast, local anesthetics not only block tumor cell migration mechanisms [36], inhibit tumor cell differentiation or proliferation, and have analgesic and anti-inflammatory properties [37], but also reduce perioperative opioid use. In an observational study

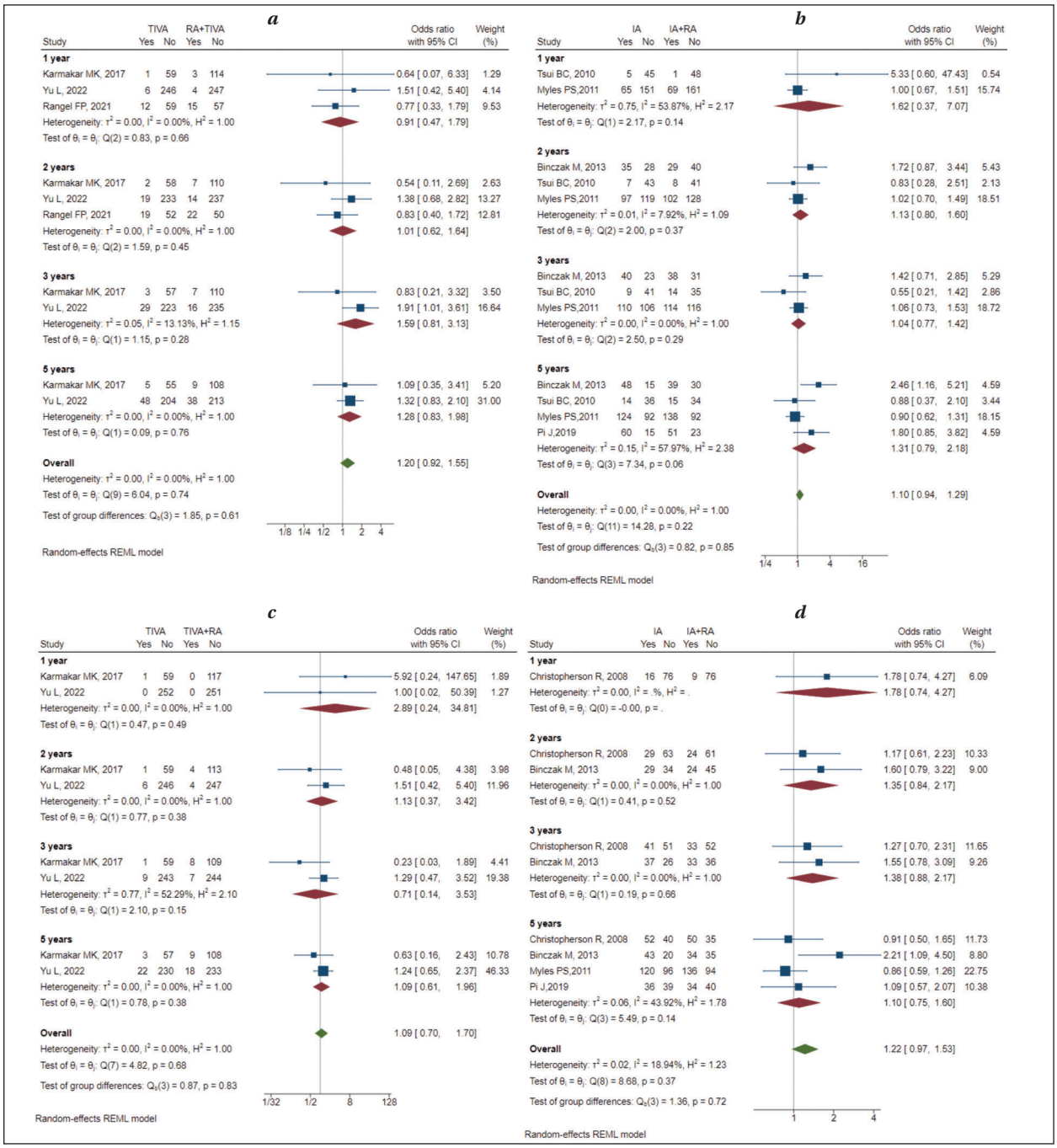

Fig. 2. Forest-plot and meta-analysis data of recurrence-free *(a, b)* and overall *(c, d)* survival in cancer patients with TIVA vs. TIVA+RA *(a, c)*, IA vs. IA+RA *(b, d)*.

Table 2. Results of the meta-analysis.

Outcome and subgroup		Papers	N, GA	N, GA+RA	OR (95% CI)	Total effect	I^2, %	Egger test
RFS	IA/IA+RA	4	404	422	1.10 (0.94–1.29)	0.27	0	*P*=0.115
	TIVA/TIVA+RA	3	381	438	1.20 (0.92–1.55)	0.17	0	*P*=0.207
OS	IA/IA+RA	4	446	458	1.22 (0.97–1.53)	0.09	19	*P*=0.003
	TIVA/TIVA+RA	2	310	366	1.09 (0.70–1.70)	0.70	0	*P*=0.577

Note. RFS — recurrence-free survival; OS — overall survival; OR — odds ratio; CI — confidence interval; GA — general anesthesia; RA — regional anesthesia; TIVA — total intravenous anesthesia; IA — inhalation anesthesia.

of 129 patients, A. K. Exadaktylos et al. showed that the control group, which received general anesthesia followed by morphine-based analgesia, had a significantly higher risk of cancer recurrence than the experimental group, which received paravertebral blockade combined with general anesthesia (*P*=0.012) [38]. However, to increase the level of evidence, additional randomized clinical trials with

Table 3. Level of evidence for the outcomes studied (GRADE approach).

Statement	D1	D2	D3	D4	D5	D6	TOTAL
The use of TIVA+RA combination in cancer patients does not lead to a change in RFS compared to TIVA	N/S (0)	Significant (–1)	Significant (–1)	Very significant (–2)	N/S (0)	No	⊕◯◯◯ Very low
The use of TIVA+RA combination in cancer patients does not lead to a change in OS, compared to TIVA	N/S (0)	N/S (0)	Выражена (–1)	Very significant (–2)	N/S (0)	No	⊕⊕◯◯ Low
The use of IA+RA combination in cancer patients does not lead to a change in RFS, compared to IA	N/S (0)	Significant (-1)	N/S (0)	Very significant (–2)	N/S (0)	No	⊕⊕◯◯ Low
The use of IA+RA combination in cancer patients does not lead to a change in OS, compared to IA	Significant (–1)	Significant (–1)	N/S (0)	Very significant (–2)	Significant (–1)	No	⊕◯◯◯ Very low

Notes. RFS — recurrence-free survival; OS — overall survival; RA — regional anesthesia; TIVA — total intravenous anesthesia; IA — inhalation anesthesia. Domains: D1 — overall risk of bias; D2 — clinical and statistical heterogeneity (inconsistency); D3 — sample inconsistency with the statement; D4 — inaccuracy; D5 — systematic publication bias; D6 — upgrading level of evidence.
0 — no downgrading of level of evidence; –1 — downgraded by 1 level; –2 — downgraded by 2 levels. N/S — not significant; N/A —not applicable. The baseline level of evidence is high.

adequate statistical power are needed to evaluate the impact of the opioid-sparing effect of regional anesthesia on long-term oncologic outcomes.

It is important to note that including trials with different types of malignancies in the analysis may distort the final results. This is because cancer survival rates can vary considerably depending on the type of tumor and the availability of radical treatment. For example, melanoma, bladder cancer, and lung cancer have 5-year survival rates of 92%, 53–77%, and 16–19%, respectively [39, 40]. Thus, M. Weng and colleagues, after performing a subgroup analysis in their study, confirmed the hypothesis of a statistically significant association between the use of neuroaxial anesthesia and improved overall survival in colorectal cancer (OR 0.653, 95% CI 0.430–0.991, *P*=0.045) [41].

Limitations. In two of the eight RCTs analyzed, the sample size reached several hundred participants, but most studies were conducted at a single medical center. The single-center nature of these studies limits their external validity, which is particularly critical in the context of intensive care, where practices may vary widely between countries. These factors could potentially bias the true effect of regional anesthesia on cancer recurrence rates.

Another significant drawback was the heterogeneity of anesthesia support in the study groups. Although the authors attempted to differentiate the groups by methods of anesthesia maintenance, such as total intravenous anesthesia and the use of inhalational anesthetics, a number of RCTs used propofol during induction in the inhalation anesthesia groups. The oncogenic potential of a tumor is known to correlate with the level of expression of hypoxia-inducible factor-1a (HIF-1a) and its subsequent effects on cell proliferation and migration, as well as the development of resistance to chemotherapy. According to some reports, propofol is able to inhibit HIF-1a activation as well as attenuate isoflurane-induced HIF-1a activation, thus partially

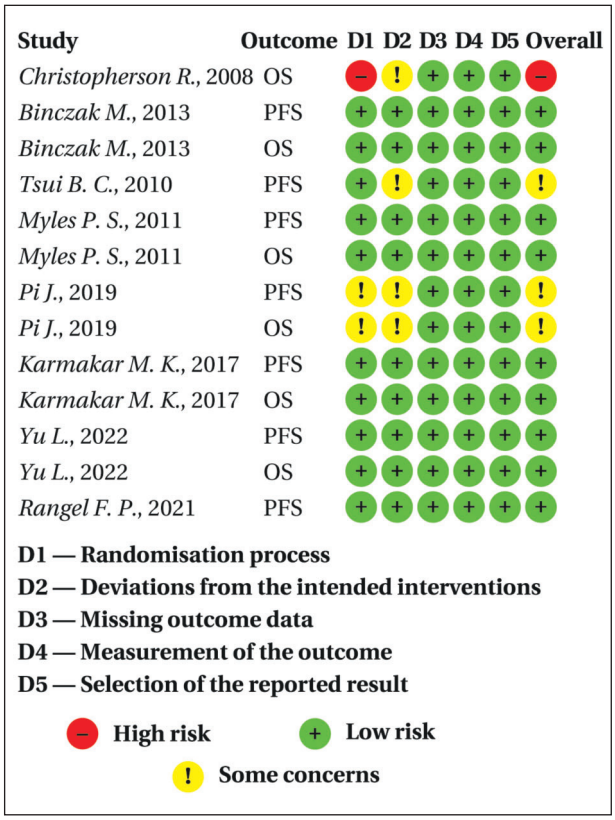

Fig. 3. Quality analysis of studies included in the meta-analysis with risk assessment of systematic bias by domain using the Cochrane RoB 2 tool.

reducing the oncogenic potential of cancer cells [42]. In addition, the postoperative analgesia regimens in each of the studies varied, ranging from the use of opioid anesthetics to no analgesia at all, which may also make it difficult to accurately assess the effects of local anesthetics.

Despite the substantial contribution of our meta-analysis to the understanding of the relationship between type of anesthesia and cancer outcomes, the current level of scientific evidence remains insufficient. New randomized trials focusing

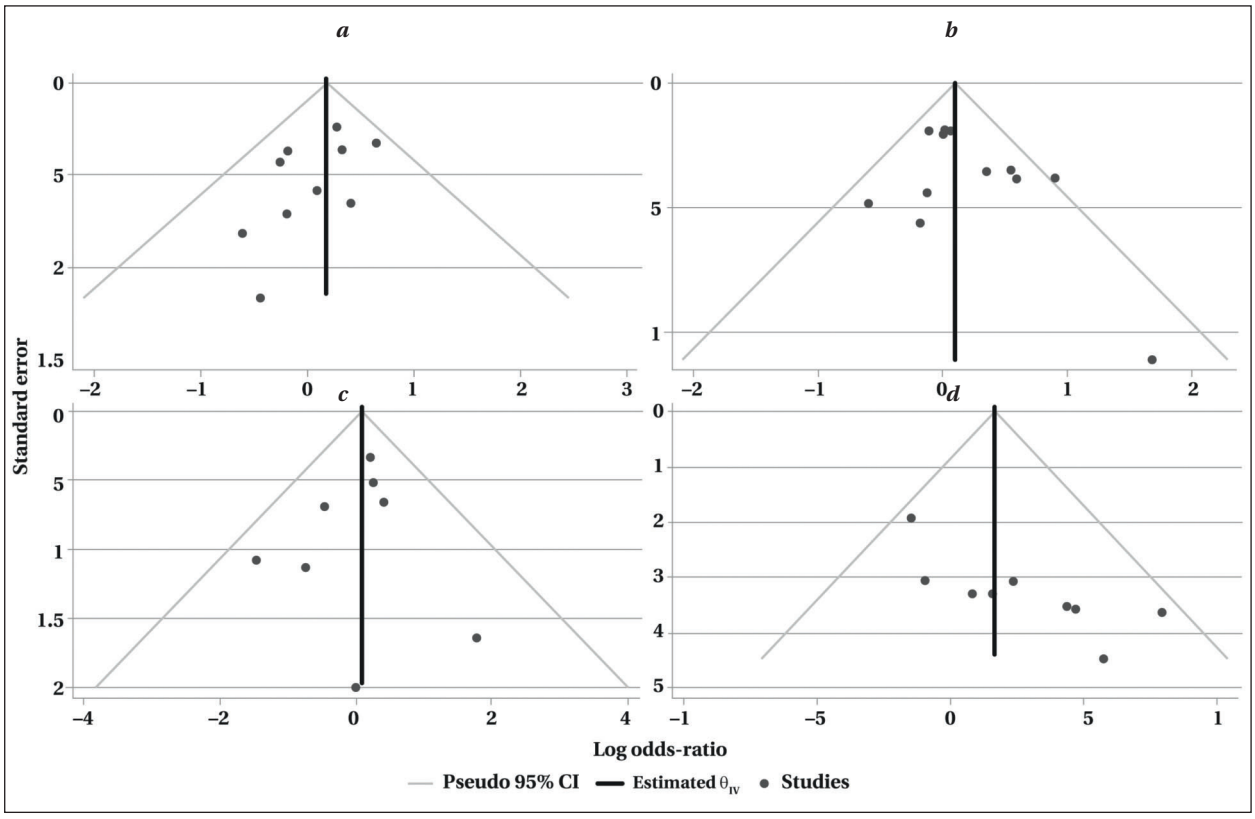

Fig. 4. Funnel plot: risk of systematic publication bias for studies comparing recurrence-free *(a, b)* and overall survival *(c, d)* for TIVA/TIVA+RA *(a, c)* and IA/IA+RA *(b, d)* in cancer

on the opioid-sparing effects of regional anesthesia are needed. Unification of anesthetic management protocols and standardization of the list of anesthetics used could greatly improve the reliability of future data. In addition, statistical survival rates may vary significantly by cancer type, necessitating a more nuanced approach in future studies.

Conclusion

A meta-analysis of 8 RCTs involving 1822 patients found no significant differences in recurrence-free and overall survival between general and combined anesthesia techniques when patient groups receiving general anesthesia were classified by the type of anesthesia used.

Thus, our findings highlight the complexity and ambiguity of the current understanding of the relationship between choice of anesthesia technique and oncologic outcomes.

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