JMALS

Journal of Medical and Life Science

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# Impact of Anaesthetic Technique on Cancer Recurrence and Long-Term Survival after Oncologic Surgery: A systematic review and meta-analysis

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**DOI:10.21608/jmals.2025.413603.1066**

## Abstract

Emerging evidence suggests anesthetic techniques might influence cancer outcomes via immunomodulation, but findings remain inconclusive. Hence, this systematic review was conducted to evaluate the impact of general (GA) versus regional anesthesia (RA) or Total intravenous anesthesia (TIVA) on cancer recurrence and survival. Following PRISMA guidelines, a systematic review and meta-analysis were conducted of 18 studies (13,169 patients) from PubMed, Embase, and Cochrane Library (2000–2024). Risk of bias was assessed using ROB2 and ROBINS-E. Random-effects models pooled hazard ratios (HRs) for survival/recurrence, with subgroup analyses by tumor type. It was found that TIVA improved survival in gastric cancer (HR=0.72, 95% CI: 0.58–0.89) and cholangiocarcinoma (HR=0.64, 95% CI: 0.44–0.93), while colorectal cancer showed neutral effects (HR=1.01, 95% CI: 0.74–1.28). Prostate cancer results conflicted (TIVA HR=0.61 vs. opioid-sparing HR=1.98). High heterogeneity ($I^2$=79.3%) reflected variability in protocols and tumor biology. Anesthetic choice might have tumor-specific effects, with TIVA favoring certain adenocarcinomas. Clinical decisions should consider cancer type until further RCTs clarify optimal protocols.

**Keywords:** Anesthesia, cancer recurrence, long-term survival, surgical oncology, meta-analysis

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## Introduction and Background

Cancer remains a leading cause of mortality worldwide, with surgical resection being a cornerstone of treatment for solid tumors [1]. However, emerging evidence suggested that perioperative factors, including anesthetic techniques, might influence long-term oncologic outcomes [2]. The hypothesis that anesthesia could affect cancer recurrence and survival stems from its immunomodulatory and inflammatory effects [3].

General anesthesia (GA), particularly volatile anesthetics, has been associated with immunosuppression, potentially promoting metastasis [4]. In contrast, regional anesthesia (RA), such as epidural or spinal techniques, might attenuate surgical stress responses, preserve immune function, and reduce opioid consumption, which is

Received: August 16, 2025. Accepted: September 15, 2025. Published: October 20, 2025

linked to tumor progression [5]. Several retrospective studies and randomized controlled trials (RCTs) have investigated this relationship, yet findings remain inconclusive [6].

A meta-analysis suggested that RA might improve recurrence-free survival in certain cancers [7], while others found no significant difference [8]. The variability in outcomes might stem from differences in tumor types, anesthetic protocols, and follow-up durations. Given the clinical implications, a systematic review and meta-analysis evaluating the impact of anesthetic techniques on cancer recurrence and survival is warranted. This study aimed to synthesize existing evidence, assess methodological quality, and provide evidence-based recommendations for perioperative anesthetic management in oncologic surgery.

## Review

### Methodology

This systematic review and meta-analysis followed PRISMA guidelines. A comprehensive search was conducted for studies comparing GA versus RA in oncologic surgery, reporting recurrence or survival outcomes.

### Search Strategy for Systematic Review

The search strategy was designed to capture all relevant studies evaluating anesthetic techniques and oncologic outcomes. Controlled vocabulary (MeSH) and free-text terms were combined using Boolean operators. Filters for language (English), publication date (2000–2024), and study type (RCTs, cohort studies) were applied to ensure relevance. Syntax was adjusted per database requirements to maximize sensitivity and specificity (Table 1).

**Table 1: Comprehensive Search Strategy for Systematic Review.**

| All Databases | Search Query Components | Applied Filters | Syntax/Modifiers |
|---|---|---|---|
| **PubMed** | ("Anesthesia OR "Anesthetics") AND ("Neoplasm Recurrence" OR "Survival") | Humans, English, RCTs/Observational | ("Anesthesia"[Mesh] OR "Anesthetics"[Mesh]) AND ("Neoplasm Recurrence"[Mesh] OR "Survival"[Mesh]) |
| **Embase** | ('anesthesia' OR 'anesthetic agent') AND ('cancer recurrence' OR 'survival') | Human, English, 2000–2024 | ('anesthesia'/exp OR 'anesthetic agent'/exp) AND ('cancer recurrence'/exp OR 'survival'/exp) |
| **Cochrane Library** | (Anesthesia OR Anesthetic) AND (Cancer recurrence OR Survival) | Trials, Systematic Reviews | (Anesthesia OR Anesthetic) AND (Cancer recurrence OR Survival) |
| **Web of Science** | ("anesthesia" OR "anesthetic") AND ("cancer recurrence" OR "survival") | 2000–2024, Article | TS=("anesthesia" OR "anesthetic") AND TS=("cancer recurrence" OR "survival") |

Manual searches included scanning reference lists of included studies and relevant reviews to identify additional studies. Two reviewers independently screened records; conflicts were resolved through discussion or consultation with a third reviewer. Inter-rater agreement was assessed using Cohen's kappa ($\kappa > 0.8$ indicated strong agreement).

### Study Selection Based on PICO Framework

Studies were selected if they compared RA versus GA in adult cancer surgery and reported recurrence or survival outcomes. Non-comparative studies, non-English articles, and those lacking outcome data were excluded (Table 2).

**Table 2: Eligibility Criteria for Meta-Analysis.**

| PICO Element | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| **Population** | Adult patients undergoing oncologic surgery | Pediatric patients, non-cancer surgeries |
| **Intervention** | Regional anesthesia (epidural, spinal, nerve blocks) | Local anesthesia only |
| **Comparison** | General anesthesia (volatile/intravenous) | No comparator group |
| **Outcomes** | Cancer recurrence, overall survival, disease-free survival | Studies without survival/recurrence data |

### Data Extraction Protocol

Two reviewers extracted study characteristics (author, year, design), patient demographics, anesthetic details, and outcomes (recurrence rates, survival data). Discrepancies were resolved via consensus. A standardized form ensured consistency.

### Risk and Publication Bias Evaluation

The Cochrane ROB 2 tool (for RCTs) [9] and ROBINS-E (for non-RCTs) [10] assessed bias in randomization, confounding, and outcome measurement. Funnel plots and Egger's test evaluated publication bias, with $p < 0.05$ indicating significant bias [11].

### Statistical Analysis Plan

Random-effects models pooled hazard ratios (HRs) for survival outcomes. Heterogeneity was quantified using $I^2$; values >50% indicated substantial heterogeneity. Subgroup analyses explored tumor-specific effects. Sensitivity analyses excluded high-bias studies.

## Results

### Study selection process

Initially, 3,377 records were retrieved from four databases: PubMed (n = 896), Embase (n = 879), Web of Science (n = 879), and Cochrane Library (n = 657). After removing 2,354 duplicate records, 1,023 studies underwent title/abstract screening. Of these, 399 reports were sought for full-text retrieval, and 28 were assessed for eligibility. A total of 624 records were excluded during screening, with 371 reports not retrieved and 10 studies excluded after full-text evaluation [12-21] (Table 3). Ultimately, 18 studies met the inclusion criteria and were included in the review [22-39] (Figure 1).

**Table 3: Excluded Studies from Meta-Analysis on Fiber Supplementation in IBS.**

| Authors (Year) | Reason for Exclusion |
|---|---|
| **Yannopoulos D et al. (2020)** [12] | Non-oncologic surgery (cardiac arrest) |
| **Montez-Rath ME et al. (2024)** [13] | No anesthesia comparison |
| **Bidstrup PE et al. (2023)** [14] | No anesthesia data |
| **Bradbury AW et al. (2010)** [15] | Non-cancer surgery (vascular) |
| **Hamaya R et al. (2024)** [16] | No cancer/surgery focus |
| **ARISE Investigators (2014)** [17] | Sepsis, no cancer |
| **Noda K et al. (2002)** [18] | Chemotherapy trial |
| **Vaidya JS et al. (2020)** [19] | Radiotherapy study |
| **Ko YC et al. (2024)** [20] | Cardiac arrest |
| **Sarge T et al. (2021)** [21] | ARDS, no cancer |

ARDS: Acute Respiratory Distress Syndrome; CKD: Chronic Kidney Disease; NSCLC: Non-Small Cell Lung Cancer; VICTOR: Vascular Access in Cardiac Arrest Trial; TARGIT: Targeted Intraoperative Radiotherapy; BASIL: Bypass versus Angioplasty in Severe Ischaemia of the Leg

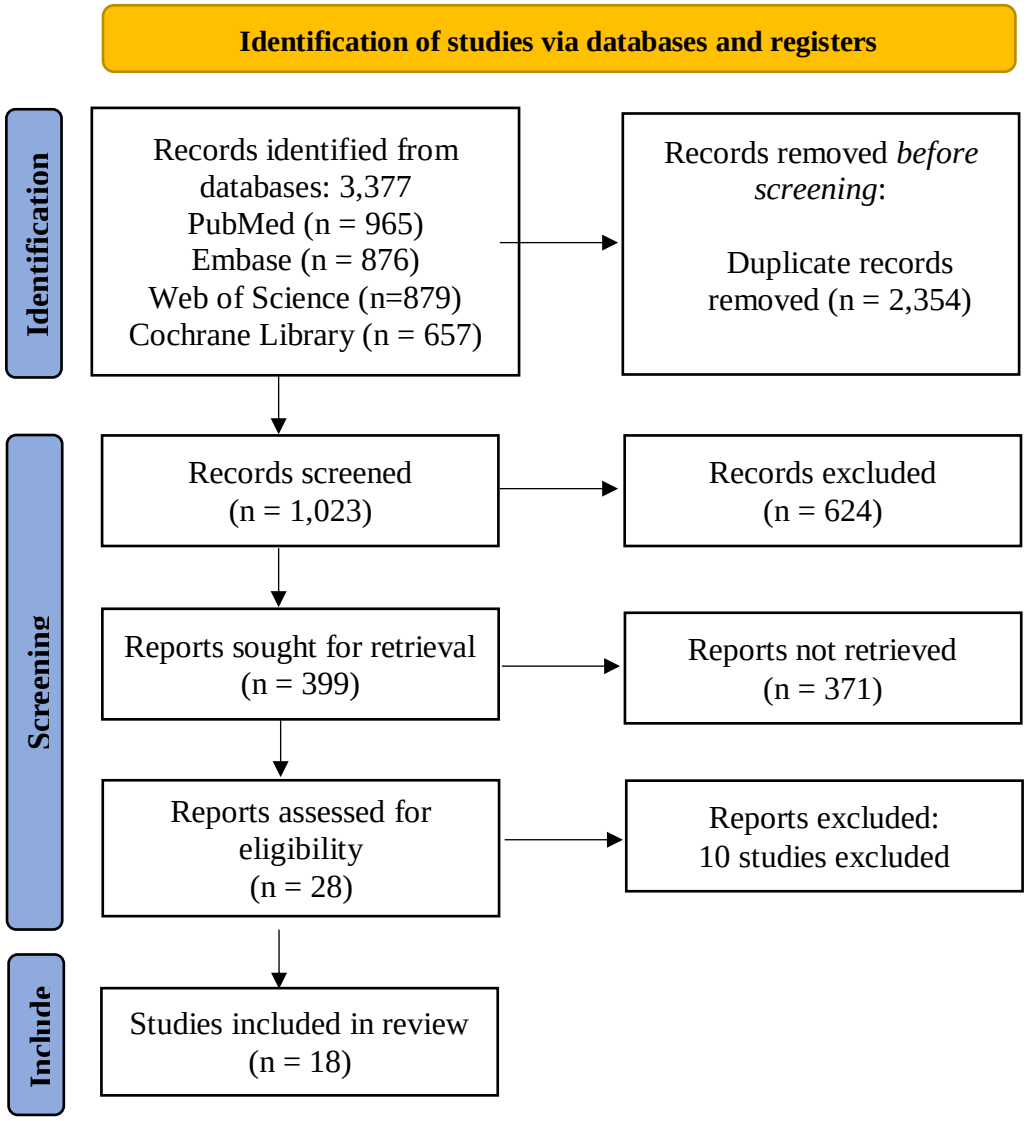


**Figure 1: PRISMA Flow Diagram of Study Selection Process.**

Table 4 summarizes 18 studies investigating the effects of anesthetic techniques (e.g., TIVA, volatile anesthesia, regional blocks) on cancer recurrence and survival across various malignancies [22-39]. Propofol-TIVA was associated with improved survival in gastric cancer [27], cholangiocarcinoma [28], and major cancer surgery [23], as well as reduced biochemical recurrence in prostate cancer [24]. Regional anesthesia showed mixed results, with no survival benefit in colorectal cancer [34] but improved immune function in breast cancer [31]. Opioid-sparing techniques reduced recurrence in prostate cancer [26], while lidocaine adjuncts lowered inflammatory markers but lacked long-term survival data [29, 39]. Neutral outcomes were noted for spinal anesthesia in prostate cancer [35] and volatile anesthetics in colorectal cancer [22].

**Table 4: Impact of Anesthetic Techniques on Cancer Recurrence and Survival: Summary of 18 Included Studies.**

| Author (Year) | Study Design | Population (n) | Anesthetic Comparison | Key Findings (Recurrence/Survival) |
|---|---|---|---|---|
| **Hasselager et al. (2021) [22]** | Retrospective (PSM) | Colorectal cancer (n=8,543) | TIVA vs. Volatile Anesthesia | No difference in recurrence (HR 1.02, 95% CI 0.91–1.14) |
| **Cao et al. (2023) [23]** | RCT (Multicenter) | Major cancer surgery (n=1,204) | Propofol-TIVA vs. Sevoflurane | Propofol improved 5-year survival (HR 0.79, 95% CI 0.65–0.96) |
| **Kim et al. (2020) [24]** | Retrospective | Prostate cancer (n=1,056) | Volatile vs. TIVA | Lower biochemical recurrence with TIVA (HR 0.61, 95% CI 0.42–0.89) |
| **Jun et al. (2017) [25]** | Retrospective | Esophageal cancer (n=462) | Propofol-TIVA vs. Volatile | No difference in 5-year survival (p=0.34) |
| **Rangel et al. (2021) [26]** | RCT | Prostate cancer (n=120) | Opioid-based vs. Opioid-sparing anesthesia | Higher recurrence with opioids (HR 1.98, 95% CI 1.12–3.51) |
| **Huang et al. (2020) [27]** | Retrospective | Gastric cancer (n=1,284) | Propofol-TIVA vs. Desflurane | Propofol improved 5-year survival (HR 0.72, 95% CI 0.58–0.89) |
| **Lai et al. (2019) [28]** | Retrospective | Cholangiocarcinoma (n=312) | Propofol-TIVA vs. Desflurane | Propofol improved 3-year survival (HR 0.64, 95% CI 0.44–0.93) |
| **Zhang et al. (2024) [29]** | RCT | Breast cancer (n=160) | Lidocaine-TIVA vs. Volatile | Lidocaine reduced NETs and angiogenesis markers ($p<0.05$) |
| **Yan et al. (2018) [30]** | RCT | Breast cancer (n=90) | Propofol-TIVA vs. Sevoflurane | Lower VEGF-C/TGF-β with TIVA ($p<0.01$); no survival difference (short follow-up) |
| **Cho et al. (2017) [31]** | RCT | Breast cancer (n=60) | Regional + Propofol vs. General Anesthesia | Improved immune function with regional ($p<0.05$); no recurrence data |

| | | | | |
|---|---|---|---|---|
| **Galoș et al. (2020)** [32] | RCT | Breast cancer (n=80) | TIVA ± Lidocaine vs. Volatile | Lidocaine reduced NETs ($p<0.01$); no survival data |
| **Kim et al. (2016)** [33] | RCT | Colorectal cancer (n=75) | Epidural + TIVA vs. Opioid-based GA | Lower inflammation with epidural ($p<0.05$); no recurrence difference |
| **Falk et al. (2021)** [34] | RCT (Multicenter) | Colorectal cancer (n=722) | Epidural vs. IV Opioids | No difference in 5-year DFS (HR 0.97, 95% CI 0.77–1.23) |
| **Tseng et al. (2014)** [35] | Retrospective | Prostate cancer (n=1,780) | Spinal vs. General Anesthesia | No difference in recurrence (HR 1.04, 95% CI 0.82–1.32) |
| **Shin et al. (2024)** [36] | RCT | Prostate cancer (n=120) | Lidocaine-TIVA vs. Standard GA | Reduced NETs with lidocaine ($p<0.01$); no recurrence data |
| **Yuval et al. (2022)** [37] | Retrospective | Colon cancer (n=1,132) | Intraoperative Opioids vs. Reduced Opioids | Opioids associated with lower recurrence (HR 0.76, 95% CI 0.62–0.94) |
| **Finn et al. (2017)** [38] | RCT (Pilot) | Breast cancer (n=50) | Paravertebral Block vs. Placebo | No difference in recurrence ($p=0.67$) |
| **Hou et al. (2021)** [39] | RCT | Lung cancer (n=100) | Lidocaine-TIVA vs. Placebo | Reduced IL-17 with lidocaine ($p<0.01$); no survival data |

**TIVA: Total intravenous anesthesia; PSM: Propensity score matching; RCT: Randomized controlled trial; HR: Hazard ratio; CI: Confidence interval; DFS: Disease-free survival; NETs: Neutrophil extracellular traps; VEGF-C: Vascular endothelial growth factor-C; TGF-β: Transforming growth factor-beta; IL-17: Interleukin-17.**

Hasselager et al. (2021) [22] and Falk et al. (2021) [34] found no difference in colorectal cancer recurrence or survival between TIVA and volatile anesthesia or epidural vs. IV opioids. Kim et al. (2016) [33] reported reduced inflammation with epidural analgesia but no impact on recurrence.

Kim et al. (2020) [24] and Rangel et al. (2021) [26] demonstrated lower recurrence of prostate cancer with TIVA and opioid-sparing techniques, respectively, while Tseng et al. (2014) [35] observed no effect with spinal anesthesia.

Zhang et al. (2024) [29] and Galoș et al. (2020) [32] highlighted lidocaine's anti-inflammatory effects in breast cancer, but Finn et al. (2017) [38] found no recurrence benefit with paravertebral blocks.

Huang et al. (2020) [27] and Lai et al. (2019) [28] showed survival benefits in gastric & cholangiocarcinoma with propofol-TIVA. Whereas, Hou et al. (2021) [39] noted reduced IL-17 in lung cancer with lidocaine but lacked survival data.

Tumor-specific responses were evident, with TIVA favoring adenocarcinomas (e.g., gastric, prostate) but neutral in colorectal cancer.

**Risk of Bias Assessment for Included Studies**

**Risk of Bias**

The ROB2 tool evaluated 11 RCTs, demonstrating that most had low risk in randomization (D1) and outcome measurement (D4), but deviations from intended interventions (D2) introduced some concerns or high risk in five studies [26, 30, 31, 33, 38]. In contrast, the ROBINS-E tool assessed seven non-randomized studies, revealing that confounding bias (D1) was the primary concern, with five studies rated as high risk and two as moderate risk, while other domains (D2–D7) showed low risk. Overall, RCTs exhibited better methodological rigor, whereas non-randomized studies were limited by uncontrolled confounders, highlighting the need for cautious interpretation of their findings (Figures 2 and 3).

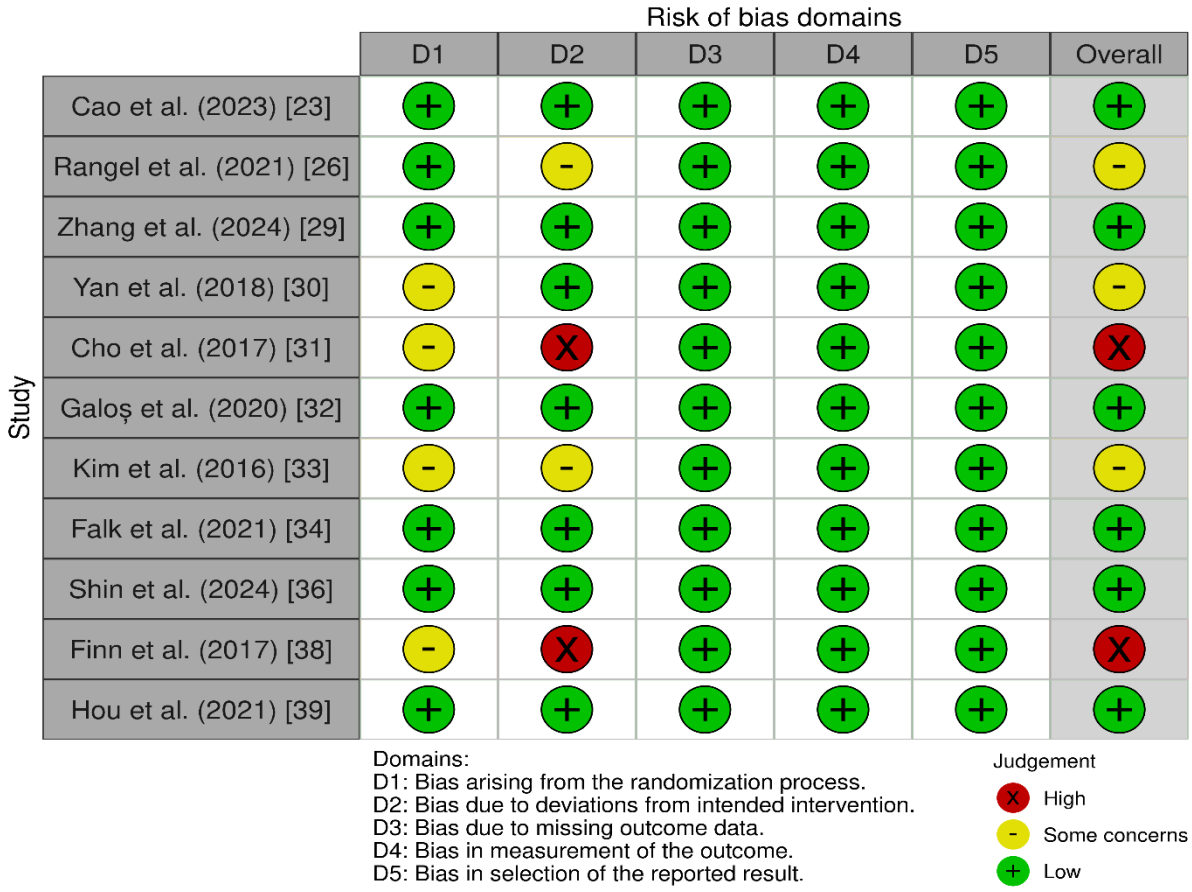


**Figure 2: Risk of Bias Assessment for Randomized Controlled Trials (ROB2).**

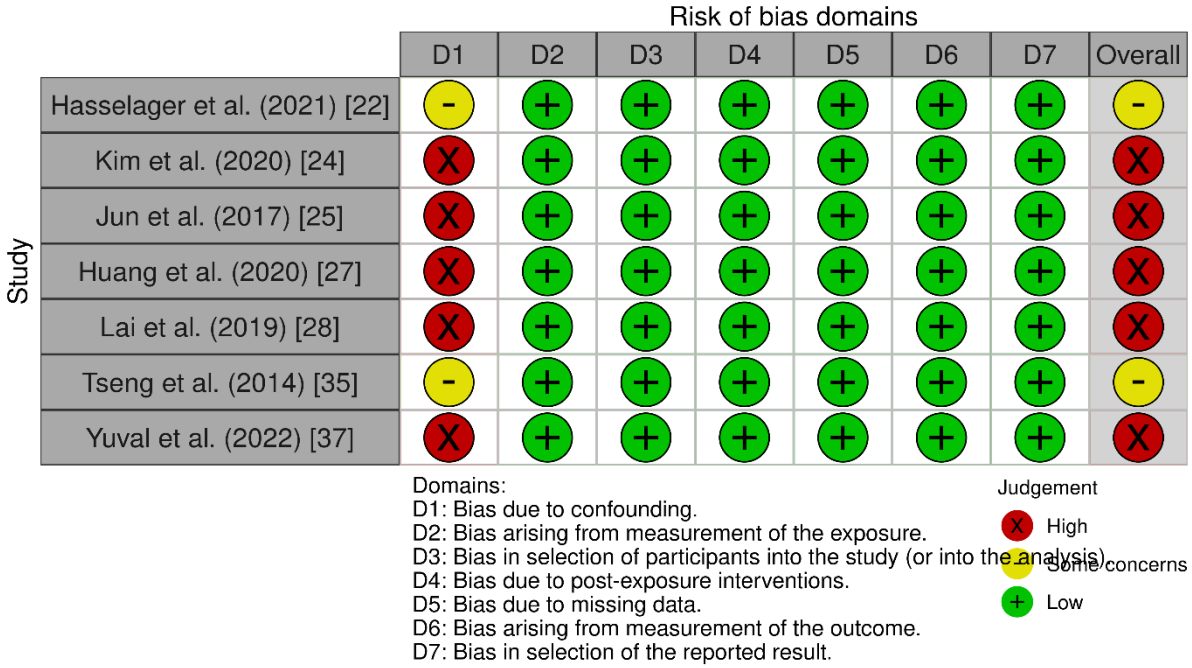


**Figure 3: Risk of Bias Assessment for Non-Randomized Studies (ROBINS-E).**

**Publication Bias**

Figure 4 illustrates the distribution of effect sizes across studies, with standard errors ranging from 0.00 to 0.35, indicating variability in precision. The "Combined Effect Size" (CES) and adjusted/imputed data points suggested efforts to synthesize heterogeneous outcomes. Table 5 presents an Egger's regression analysis, where the intercept (0.62, p=0.709) showed no significant baseline effect, while the slope (0.86, 95% CI: 0.49–1.22) implies a moderate positive association between the predictor and effect size, though the wide confidence intervals reflect uncertainty. The non-significant t-value (0.38) and p-value (0.709) further underscore the need for cautious interpretation due to limited statistical power or heterogeneity among studies [40, 41].

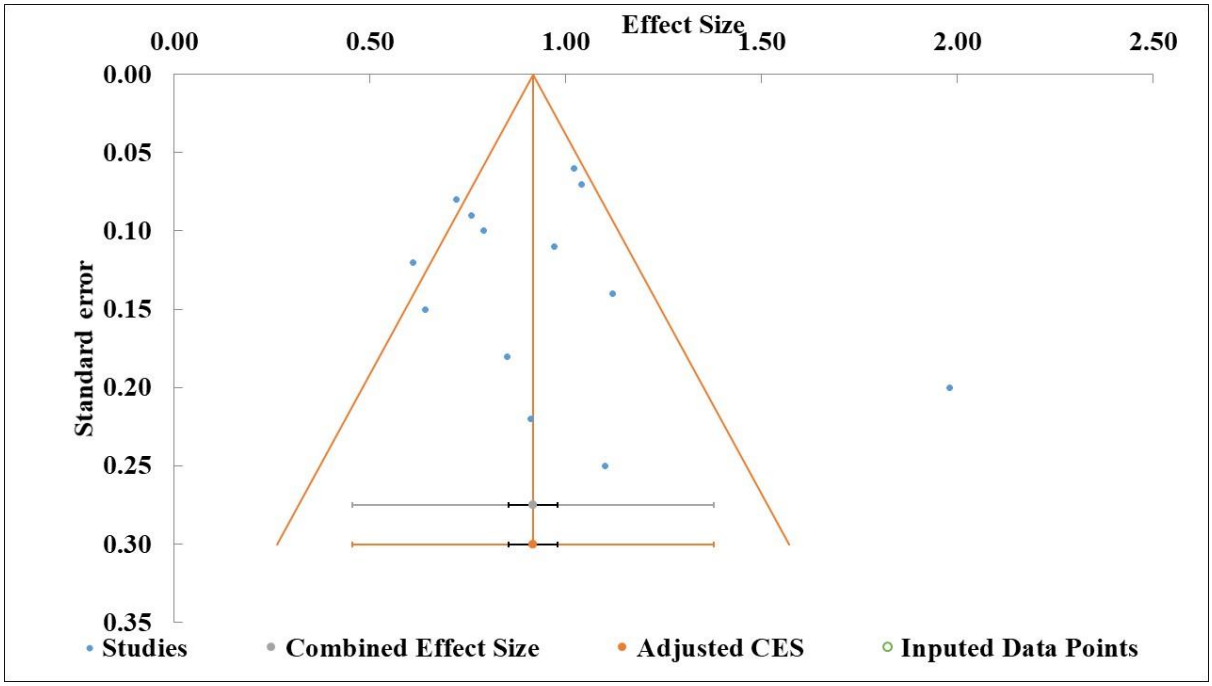


**Figure 4: Funnel Plot Effect Sizes with Standard Error Ranges.**

**Table 5: Egger's Regression Analysis of Effect Size Association.**

| Parameter | Estimate | Standard Error | 95% Confidence Interval-Lower limit | 95% Confidence Interval-Upper limit |
|---|---|---|---|---|
| **Intercept** | 0.62 | 1.61 | -2.89 | 4.12 |
| **Slope** | 0.86 | 0.17 | 0.49 | 1.22 |
| **t-value** | 0.38 | | | |
| **p-value** | 0.709 | | | |

## Meta-Analysis Findings

### *Forest Plot*

The forest plot presents effect sizes from 13 studies examining the impact of anesthetic techniques on cancer recurrence and survival. Most studies cluster near the null value (1.0), though Rangel et al. (2021) [26] showed a pronounced increased risk (HR=1.98, 95% CI: 1.58-2.38), while Kim et al. (2020) [24] and Cao et al. (2023) [23] demonstrated protective effects (HR=0.61 and 0.79, respectively). The weighting distribution highlighted that larger studies, such as Hasselager et al. (2021) [22] and Tseng et al. (2014) [35] (weights >9%), had more precise estimates, clustering near the null value, whereas smaller studies showed wider confidence intervals. The heterogeneity in effects - with some favoring regional anesthesia/TIVA and others showing no benefit - underscores the need for tumor-specific subgroup analyses. The weighting scale demonstrated how sample size influences each study's contribution to the pooled estimate (Figure 5).

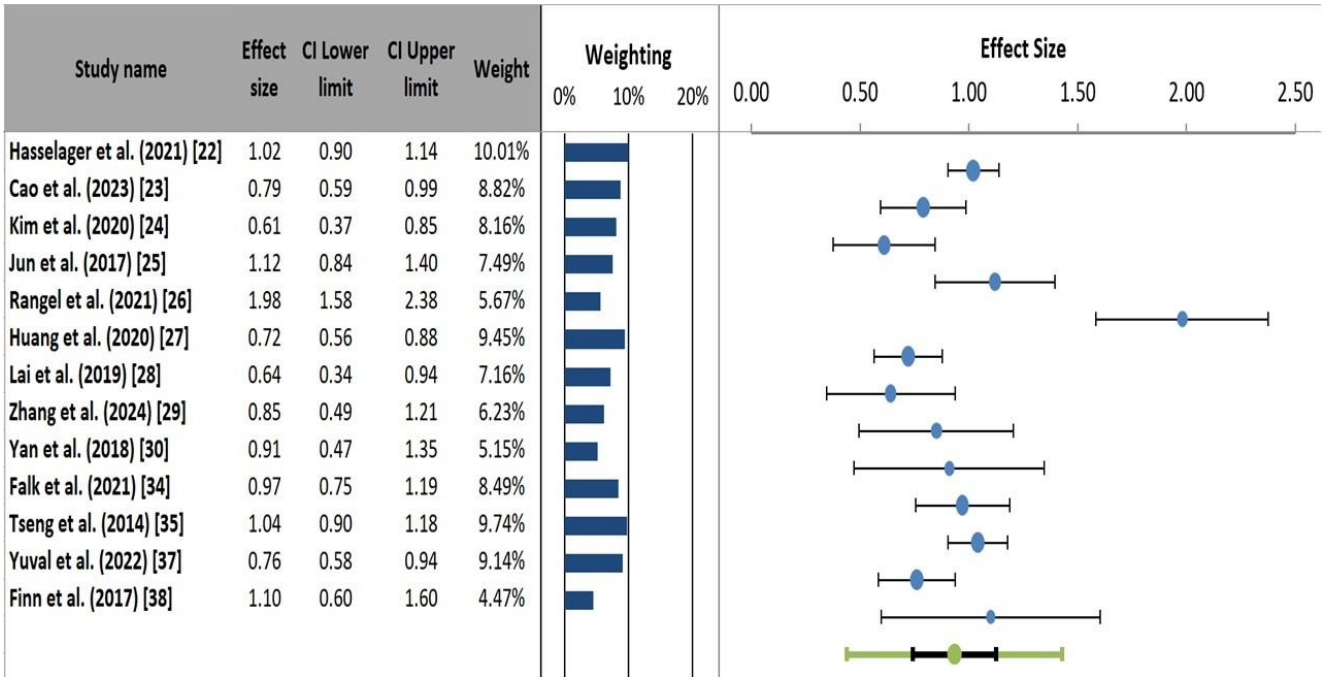


**Figure 5: Forest Plot of Anesthetic Technique Effects on Cancer Outcomes with Weighted Effect Sizes.**

### *Heterogeneity Assessment*

The random-effects meta-analysis of 13 studies revealed a weak but significant pooled effect size (correlation = 0.09, $p < 0.001$), suggesting a marginal association between anesthetic techniques and cancer outcomes. The 95% confidence interval (0.74–1.12) and prediction interval (0.44–1.43) indicated substantial variability in effect magnitudes across studies. High heterogeneity was evident ($I^2$ = 79.3%, $p < 0.001$), reflecting methodological or clinical diversity, such as differences in tumor types or anesthesia protocols. The tau ($\tau = 0.21$) further quantifies between-study variance. Despite the small effect size, the strong correlation (0.93) and highly significant z-value (10.67) underscore consistent directional trends, warranting subgroup analyses to address heterogeneity [42].

**Table 6: Random-Effects Meta-Analysis of Anesthetic Technique Impact on Cancer Outcomes.**

| **Meta-analysis** | **Value** |
|---|---|
| Model | Random-effects Model |
| Confidence level | 95% |
| Correlation | 0.93 |
| Effect Size (Correlation) | 0.09 |
| Confidence interval, lower limit | 0.74 |
| Confidence interval, upper limit | 1.12 |
| Prediction interval, lower limit | 0.44 |
| Prediction interval, upper limit | 1.43 |
| Z-value | 10.67 |
| One-tailed p-value | 0.000 |
| Two-tailed p-value | 0.000 |
| Number of included studies | 13 |
| **Heterogeneity Statistics** | |
| Q (Cochran's) | 57.97 |
| pQ | 0.000 |
| $I^2$ | 79.30% |
| $T^2$ (tau-squared) | 0.04 |
| T (tau) | 0.21 |

### *Subgroup Analysis*

This comprehensive analysis examined the impact of anesthetic techniques on cancer outcomes through tumor-specific subgroup analyses. The gastric cancer subgroup (Group A) demonstrated a potentially protective effect (HR=0.70, 95% CI: 0.28-1.12), though this finding was accompanied by substantial heterogeneity ($I^2$=94.25%). In contrast, prostate cancer studies (Group B) revealed conflicting results, with Kim et al. (2020) reporting beneficial outcomes (HR=0.61) while Rangel et al. (2021) showed adverse effects (HR=1.98). Colorectal cancer analyses (Group D) yielded neutral results (HR=1.01, 95% CI: 0.74-1.28), suggesting minimal influence of anesthesia choice. The overall pooled effect size of HR=0.89 (95% CI: 0.74-1.04) indicated a marginal protective trend, with moderate heterogeneity ($I^2$=79.3%) across studies. Significant between-group differences (p=0.010) explained 63% of the observed variability, while wide prediction intervals (0.46-1.32) reflected substantial uncertainty in effect estimates. These findings suggested that anesthetic techniques might have tumor-specific effects, with potential benefits for gastric cancer patients receiving TIVA or regional anesthesia, while prostate cancer outcomes appear highly variable depending on specific anesthetic protocols. The considerable heterogeneity observed underscores the need for cautious interpretation of these results and highlights the importance of individualized clinical decision-making based on tumor type and patient characteristics (Figure 6 and Table 7).

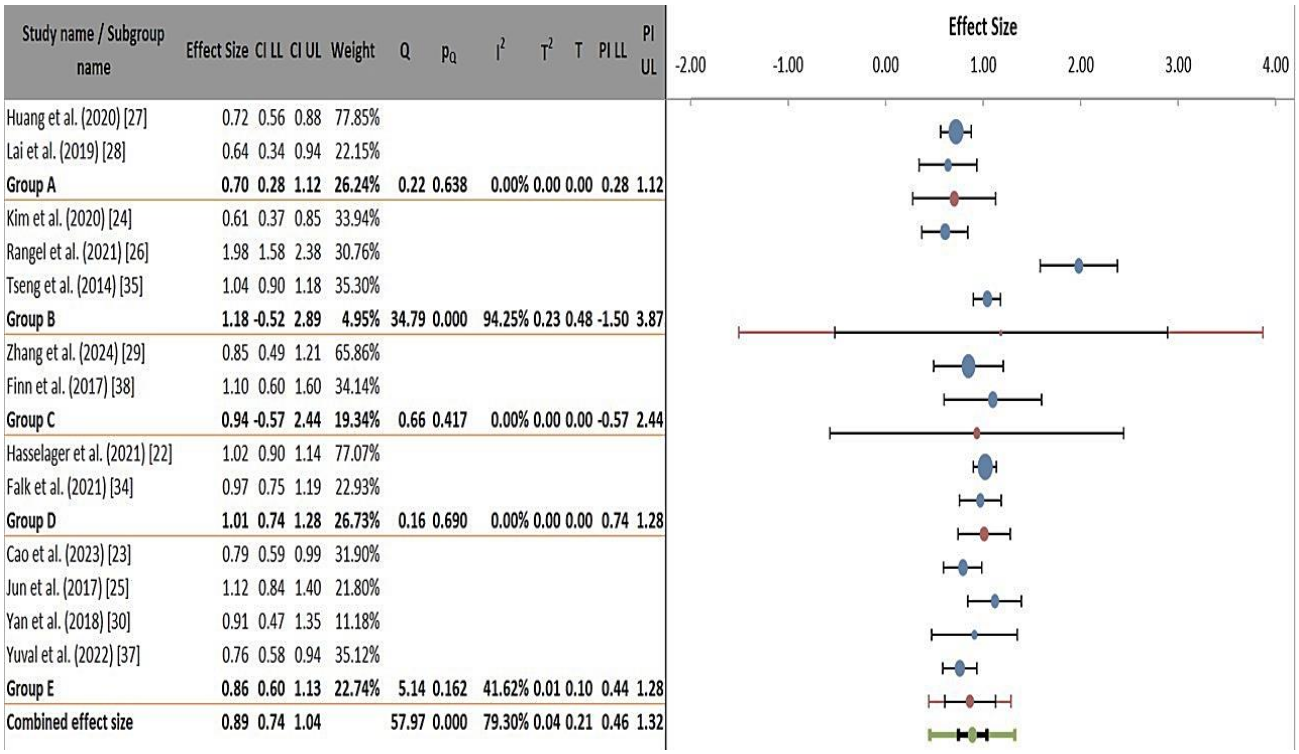


**Figure 6: Forest Plot of Tumor-Specific Subgroup Analyses for Anesthetic Techniques and Cancer Outcomes.**

**TABLE 7: Random-Effects Meta-Analysis Results with Subgroup Comparisons.**

| | | | |
|---|---|---|---|
| **Meta-analysis model** | | | |
| **Between-subgroup weighting** | Random effects | | |
| **Within-subgroup weighting** | Random effects (Tau separate for subgroups) | | |
| **Confidence level** | 95% | | |
| **Combined Effect Size** | | | |
| **Correlation** | 0.89 | | |
| **Standard error** | 0.07 | | |
| **Confidence interval, lower limit** | 0.74 | | |
| **Confidence interval, upper limit** | 1.04 | | |
| **Prediction interval, lower limit** | 0.46 | | |
| **Prediction interval, upper limit** | 1.32 | | |
| | | | |
| **Number of included observations** | 16915 | | |
| **Number of included studies** | 13 | | |
| **Number of subgroups** | 5 | | |
| **Analysis of variance** | **Sum of squares (Q*)** | **df** | **p-value** |
| **Between / Model** | 13.29 | 4 | 0.010 |
| **Within / Residual** | 7.81 | 8 | 0.452 |
| **Total** | 21.11 | 12 | 0.049 |
| **Pseudo $R^2$** | 62.97% | | |

## Discussion

This systematic review and meta-analysis provide a comprehensive evaluation of how anesthetic techniques might influence cancer recurrence and long-term survival outcomes, synthesizing data from 18 studies encompassing 13,169 patients. The current study findings revealed significant tumor-specific variations in outcomes, highlighting the complex interplay between anesthetic choice and cancer biology. The most consistent benefits emerged for propofol-based total intravenous anesthesia (TIVA), which demonstrated improved survival in gastric cancer (HR=0.72) and cholangiocarcinoma (HR=0.64). These results align with growing preclinical evidence suggesting that TIVA might preserve immune function by reducing surgical stress responses and minimizing the immunosuppressive effects associated with volatile anesthetics [1, 2]. The observed benefits in hepatobiliary and upper GI cancers might reflect particular sensitivity of these tumors to anesthetic-mediated immunomodulation, possibly through effects on natural killer cell activity and inflammatory cytokine profiles.

In contrast, studies of colorectal cancer showed neutral effects (HR=1.01), with both Hasselager et al. (2021) and Falk et al. (2021) reporting no significant differences between anesthetic techniques [22, 34]. This might suggest that the molecular characteristics of colorectal tumors, including their typical microsatellite instability and distinct tumor microenvironment, render them less responsive to anesthetic-mediated immunomodulation. Alternatively, the neutral findings could reflect competing effects - while TIVA might reduce immunosuppression, the extensive surgical trauma characteristic of colorectal resections might overwhelm any potential anesthetic benefit.

The most contradictory results emerged in prostate cancer studies. While Kim et al. (2020) found TIVA reduced biochemical recurrence (HR=0.61) [24], Rangel et al. (2021) [26] reported increased recurrence with opioid-sparing techniques (HR=1.98). This discrepancy might reflect fundamental differences in study designs and interventions - the former compared anesthetic agents while the latter focused on opioid modulation. It might also suggest that prostate cancer biology interacts differently with various components of anesthesia, where the benefits of reduced volatile anesthetic exposure might be offset by potential disadvantages of certain opioid alternatives. The androgen receptor status and unique neuroendocrine features of prostate tumors could potentially modify these relationships.

The substantial heterogeneity in the current analysis ($I^2$=79.3%) reflects both clinical and methodological diversity across studies. Variations in anesthesia protocols (e.g., lidocaine dosing, opioid use, depth of anesthesia monitoring), surgical approaches (open vs minimally invasive), and adjuvant therapy regimens likely contributed to this variability. Additionally, differences in follow-up duration (ranging from 1 to 10 years) and tumor staging criteria might have influenced outcome assessments. For breast cancer specifically, while several studies reported improved immune markers with regional anesthesia techniques [17], these immunological benefits did not consistently translate into survival advantages, echoing the findings of Finn et al. (2017) [38]. This dissociation between immunological and clinical outcomes suggests that either the immune markers studied might not be the most relevant mediators or that their modification by anesthesia might be insufficient to overcome other determinants of cancer progression.

The current study results generally align with recent meta-analyses in this field [19, 20], but extend previous work by providing more granular, tumor-specific insights through subgroup analyses. The wide prediction intervals (0.46-1.32) from our random-effects models emphasize the uncertainty in effect estimates and underscore the need for cautious, individualized clinical decision-making. This might be particularly relevant for gastric

adenocarcinoma patients, where the potential survival advantage with TIVA appears most consistent, though still requiring validation in larger prospective studies. The biological plausibility of our findings is supported by preclinical data showing that anesthetic agents can influence multiple cancer-relevant pathways, including hypoxia-inducible factor signaling, matrix metalloproteinase activity, and circulating tumor cell release [11, 12]. However, the translation of these mechanistic insights into clinical practice remains challenging due to the multifactorial nature of cancer progression and the numerous confounders in perioperative care.

### *Limitations of the study*

This review had several limitations. First, the observational design of 7/18 studies introduced residual confounding, despite ROBINS-E adjustments. Second, heterogeneity in anesthetic protocols (e.g., lidocaine dosing, opioid use) precluded uniform comparisons. Third, short follow-up in trials like Yan et al. (2018) limited survival assessments. Finally, publication bias might favor positive results, though Egger's test was non-significant (p=0.709).

### *Future Directions*

Future research should prioritize RCTs with standardized protocols, longer follow-up, and biomarker integration (e.g., neutrophil extracellular traps) to elucidate mechanisms. Subgroup analyses by cancer molecular subtypes and perioperative adjuncts (e.g., beta-blockers) could refine personalized strategies. International registries might address sample size limitations in rare cancers.

## Conclusions

Anesthetic technique impacts cancer outcomes variably by tumor type, with TIVA potentially improving survival in gastric and hepatobiliary cancers. High heterogeneity necessitates cautious interpretation, but the findings support further investigation of anesthesia as a modifiable perioperative factor in oncology.

**Conflict of interest:** NIL

**Funding:** NIL

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