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Original Article

Anaesthesia Section

Effects of Anaesthetic Techniques on Cancer Recurrence and Survival: A Systematic Review and Meta-analysis

HEMLATA[1], APARNA SHUKLA[2], REETU VERMA[3]

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ABSTRACT

Introduction: Many anaesthetic agents and techniques are used in surgical oncology, yet their effects on cancer cells remain inconclusive. Some studies suggest that propofol-based Total Intravenous Anaesthesia (TIVA) and regional anaesthetic techniques may protect against cancer progression, while volatile anaesthetics and high-dose opioids could increase recurrence. Other research indicates that anaesthetics may have no effect.

Aim: To evaluate the impact of General Anaesthesia (GA) supplemented with Regional Analgesia (RA) on Overall Survival (OS) in adult cancer surgery patients, as well as the effects of TIVA versus Inhalational Anaesthesia (INHA) on OS.

Materials and Methods: The present systematic review and meta-analysis was conducted at King George's Medical University, Lucknow, Uttar Pradesh, India, PUBMED/MEDLINE, EMBASE/Emtree, Google Scholar, and ResearchGate were searched. Original retrospective studies from 2005 to 2020 on adult cancer surgeries were included. Eligible studies involved primary cancer surgeries under general anaesthesia (TIVA or volatile) alone or with regional anaesthesia. Only studies published in English and providing numeric Hazard Ratios (HR) were considered. The selected studies were divided into two groups: 10 studies comparing GA with or without RA, and 13 studies comparing TIVA versus INHA. Forest plots were generated to analyse pooled data, and Begg's funnel plots were used to assess publication bias. The Risk Ratio (RR) was used to measure dichotomous outcomes with 95% Confidence Intervals (CI). Heterogeneity was assessed using the τ^2 statistic, and a fixed-effects model was applied. The risk of bias in included studies was assessed using the Newcastle-Ottawa Scale (NOS). The GRADE system was applied to ascertain the level of evidence.

Results: A total of 23 retrospective studies involving 67,550 patients were included. In the GA+RA versus GA comparison (10 studies, 46,425 patients), GA+RA was associated with improved overall survival (RR=0.91, 95% CI: 0.89-0.92) but showed no significant difference in recurrence-free survival (RR=1.01, 95% CI: 1.00-1.02). In the TIVA versus INHA comparison (13 studies, 21,125 patients), TIVA was associated with modestly better overall survival (RR=1.11, 95% CI: 1.09-1.13) and recurrence-free survival (RR=1.06, 95% CI: 1.04-1.08). Heterogeneity was low to moderate, and the quality of evidence was graded as low to moderate due to the retrospective design. All 23 studies were evaluated using NOS, with scores ranging from 6 to 9. Most studies scored 7 or higher, indicating moderate to high quality. Evidence certainty was rated as low to moderate for both OS and RFS outcomes across comparisons due to the retrospective nature of the studies.

Conclusion: This study provides evidence that anaesthetic technique may impact long-term outcomes in patients undergoing cancer surgery. General anaesthesia combined with regional analgesia (GA+RA) was associated with improved OS, although no significant difference was observed in Recurrence-Free Survival (RFS). Additionally, TIVA showed a survival benefit over INHA, with improvements in both OS and RFS. Despite these findings, the overall certainty of evidence is limited by the retrospective design of the included studies.

Keywords: Anaesthesia, General anaesthesia, Inhalation, Long-term survival, Progression-free survival, Regional

INTRODUCTION

The incidence of carcinoma is increasing steadily. Total cancer cases in India have risen dramatically over the past decade, from 979,786 cases in 2010 to 1,148,757 cases in 2020 [1]. The worldwide situation is similarly concerning. This trend has led to advancements in cancer surgeries and associated anaesthetic techniques. Recent studies suggest that many perioperative factors influence both long- and short-term outcomes in cancer patients. These factors include surgical techniques, types of anaesthetic techniques, and the drugs used.

A literature search revealed contradictory results regarding the effects of anaesthetic techniques and drugs on outcomes in cancer patients. Exadaktylos AK et al., reported that the use of a paravertebral block along with GA in primary breast cancer surgery reduces the risk of recurrence or metastasis during the early postoperative years [2]. Similarly, Christopherson R et al., observed that epidural supplementation was associated with improved RFS after colon carcinoma surgery [3]. However, Heaney A and Buggy DJ, found no association between anaesthetic techniques and cancer recurrence or metastasis [4].

Given these contradictory and inconclusive findings [2-4], this systematic review and meta-analysis was planned to determine whether anaesthetic techniques or drugs affect OS RFS in adult patients.

In this systematic review and meta-analysis, studies evaluating the effect of anaesthetic techniques on long-term and/or short-term cancer outcomes, specifically RFS and OS, were included.

Objectives

1. To compare the effect of general anaesthesia combined with regional analgesia (GA+RA) versus General Anaesthesia (GA) alone on Overall Survival (OS) in adult patients undergoing cancer surgery.
2. To assess the impact of GA+RA versus GA alone on RFS in the same population.
3. To evaluate the effect of TIVA versus Inhalational Anaesthesia (INHA) on OS in adult cancer surgery patients.
4. To determine the effect of TIVA versus INHA on RFS following cancer surgery.

5. To assess the quality and level of evidence across included studies using standardised tools (Newcastle-Ottawa Scale and GRADE system).

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted following the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [5]. The review protocol was not registered in a publicly accessible database.

Eligibility Criteria

Studies were included based on the following criteria:

- **Study design:** Retrospective cohort studies
- **Population:** Adult patients undergoing primary cancer surgery under general anaesthesia
- **Interventions:** Use of TIVA, INHA, or GA+RA
- **Outcomes:** Cancer recurrence, RFS, OS, or cancer-specific survival
- **Language:** English
- **Publication years:** 2005-2020

Studies were excluded if they:

- Involved surgery for recurrent cancer
- Used a combination of TIVA and INHA during maintenance
- Were reviews, meta-analyses, editorials, commentaries, or animal studies

The literature search strategy is summarised in [Table/Fig-1].

Database searched	Search terms used	Filters applied	Time frame
PubMed/MEDLINE	("Tumour" OR "Cancer" OR "Malignancy" OR "Neoplasm") AND ("TIVA" OR "Propofol" OR "Intravenous anaesthesia" OR "Target controlled infusion") AND ("Inhalational anaesthesia" OR "Volatile anaesthetics" OR "Sevoflurane" OR "Isoflurane") AND ("Regional analgesia" AND/OR "General anaesthesia") AND ("Cancer recurrence" AND/OR "Recurrence-free survival" AND/OR "Overall survival" AND/OR "Cancer-specific survival")	English language, Human studies	2005-2020
EMBASE/Emtree	Same keyword combinations as above, adapted to Emtree terms	English language, Human studies	2005-2020
Google scholar	Broad keyword combinations with Boolean operators (same as above)	English language	2005-2020
Research gate	Targeted keyword searches using combinations of terms related to anaesthesia and cancer outcomes	English language	2005-2020
Manual reference search	Screening of reference lists from all included articles	NA	2005-2020

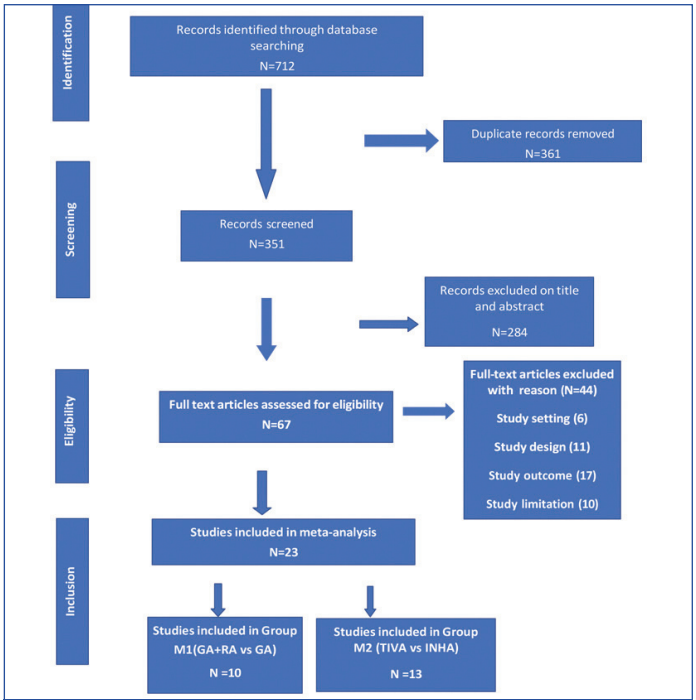
[Table/fig-1]: Literature search strategy.

Study Selection

After removing duplicates, titles and abstracts were screened for relevance. Full-text articles were then reviewed to confirm eligibility. Two independent reviewers (AS and RV) performed the selection process, and discrepancies were resolved through discussion with a third reviewer (H). A PRISMA flow diagram [Table/Fig-2] was used to document the study selection process.

Data Collection Process

Data were independently extracted by two reviewers (AS and HH) using a standardised data extraction form. Disagreements were resolved by consensus or third-party adjudication (RV).



[Table/fig-2]: PRISMA flowchart.

Data Items

The following data were extracted:

- Author(s) and year of publication
- Study design and duration
- Sample size and patient demographics
- Type of surgery and anaesthetic technique
- Reported outcomes: OS, RFS, cancer recurrence
- Hazard Ratios (HR) and 95% Confidence Intervals (CI)
- Statistical adjustments (e.g., propensity score matching)

Effect Measures

Hazard Ratios (HR) with 95% Confidence Intervals (CI) were the primary summary measures. When both unadjusted and adjusted HRs were reported, the most fully adjusted HR was extracted for analysis.

Synthesis Methods

Meta-analysis was performed using Review Manager (RevMan v5). A random-effects model was used for pooled estimates due to expected heterogeneity.

- Heterogeneity was assessed using I^2 statistics and τ^2 values.
- Pooled Risk Ratios (RR) were calculated for OS and RFS.
- A p-value <0.05 was considered statistically significant.
- Publication bias was assessed using funnel plots.

Risk of Bias and Level of Evidence

Risk of bias was assessed using a modified version of the NOS [6]. Studies were evaluated for:

- Selection bias
- Information bias
- Exposure misclassification
- Reporting bias

Begg's funnel plots were visually inspected to evaluate potential publication bias. The GRADE system [7] was applied to determine the level of evidence, categorising it as high, moderate, low, or very low based on study design, consistency, directness, precision, and risk of bias.

[Table/Fig-3] summarises the quantitative assessment for meta-analysis The 23 included studies were divided into two groups:

Parameter	GA+RA vs GA alone	TIVA vs INHA
Number of studies included	10 studies	13 studies
Total number of patients analysed	46,425	21,125
Primary outcome measured	Overall Survival (OS)	Overall Survival (OS)
Secondary outcome measured	Recurrence-Free Survival (RFS)	Recurrence-Free Survival (RFS)
Pooled Risk Ratio (RR)-OS	0.91 (95% CI: 0.89-0.92)	1.11 (95% CI: 1.09-1.13)
Pooled Risk Ratio (RR)-RFS	1.01 (95% CI: 1.00-1.02)	1.06 (95% CI: 1.04-1.08)
Statistical model used	Fixed effect model	Fixed effect model
Heterogeneity (τ^2) assessment	Low to moderate (reported)	Low to moderate (reported)
Publication bias assessment	Begg's funnel plot	Begg's funnel plot
Risk of bias assessment tool	Newcastle-Ottawa Scale (NOS)	Newcastle-Ottawa Scale (NOS)
Evidence grading system applied	GRADE	GRADE
Overall quality of evidence	Low to moderate (due to retrospective nature)	Low to moderate (due to retrospective nature)
Types of surgeries included	Colorectal, prostate, renal, bladder, gastro-oesophageal, hepatobiliary	Breast, colon, gastric, liver, rectal, lung, brain
Time period of included studies	2005-2020	2005-2020

[Table/Fig-3]: Quantitative assessment for meta-analysis.

Group M1 (n=10 studies): GA with or without regional anaesthesia

Group M2 (n=13 studies): TIVA versus INHA.

[Table/Fig-4] summarises study characteristics of the included studies [3,8-29].

S. No.	Author	Type of study and anaesthesia	Time period	Type of surgery	Outcome measures
1	Christopherson R et al., [3]	Retrospective [GA Vs GA with RA]	1992-1994	Intra-abdominal aortic, gastric, biliary or colon cancer surgery	OS
2	Gottschalk A et al., [8]	Retrospective [GA Vs GA with RA]	2000-2007	Colorectal cancer surgery	RFS
3	Wuethrich PY et al., [9]	Retrospective [GA Vs GA with RA]	1994-2000	Prostate cancer surgery	RFS, CSS, OS, Clinical progression-free survival
4	Tsui BC et al., [10]	Retrospective [GA Vs GA with RA]	2000-2001	Radical prostatectomy	RFS
5	Gupta A et al., [11]	Retrospective [GA Vs GA with RA]	2004-2008	Colon CA, Rectal CA	OS
6	Cummings KC 3rd et al., [12]	Retrospective [GA Vs GA with RA]	Year not provided	Colorectal CA	OS, RFS
7	Wuethrich PY et al., [13]	Retrospective [GA Vs GA with RA]	1994-2000	Prostatic carcinoma	RFS-Local, RFS-Distant, CSS, OS
8	Enlund M et al., [14]	Retrospective	1997-2010	Colon, rectum, breast	OS
9	Hiller JG et al., [15]	Retrospective [GA Vs GA with RA]	2005-2010	Gastro-oesophageal cancer surgery	OS, RFS
10	Wigmore TJ et al., [16]	Retrospective cohort study [TIVA Vs INHA]	2010-2013	Solid tumours	OS
11	Kim MH et al., [17]	Retrospective [TIVA Vs INHA]	2005-2010	CA breast	RFS, OS
12	Jun IJ et al., [18]	Retrospective	2005-2015	Esophageal CA	RFS, OS
13	Kovac E et al., [19]	Retrospective [GA Vs GA with RA]	1994-2008	Renal cell carcinoma	CSS and OS
14	Chipollini J et al., [20]	Retrospective [GA Vs GA with RA]	2008-2012	CA bladder-nonmetastatic urothelial	RFS and CSS
15	Oh TK et al., [21]	Retrospective	2003-2012	Non-small cell lung carcinoma	RFS, OS
16	Zheng X et al., [22]	Retrospective	2007-2012	Gastric carcinoma surgery	OS
17	Wu ZF et al., [23]	Retrospective	2005-2014	Colon cancer surgery	OS
18	Lai HC et al., [24]	Retrospective	2005-2014	Hepatocellular carcinoma	RFS, OS
19	Yoo S et al., [25]	Retrospective cohort study [TIVA Vs INHA]	2005-2013	CA breast	RFS, OS
20	Hong B et al., [26]	Retrospective [TIVA Vs INHA]	2006-2009	CA gastric, lung, liver, colon, breast	OS
21	Huang YH et al., [27]	Retrospective cohort study [TIVA Vs INHA]	2006-2010	CA breast	OS
22	Dong J et al., [28]	Retrospective [TIVA Vs INHA]	2012-2016	Supratentorial high grade glioma	Progression-free survival, OS
23	Shiono S et al., [29]	Retrospective [TIVA Vs INHA]	2008-2012	CA breast	RFS

[Table/Fig-4]: Studies included for systematic review and meta-analysis [3,8-29].
OS: Overall survival; RFS: Recurrence-free survival; CSS: Cancer-specific survival

RESULTS

A total of 23 studies were included in the analysis. [Table/Fig-5] shows group M1 and [Table/Fig-6] shows group M2.

These studies collectively included over 73,000 patients undergoing various cancer surgeries. All studies employed matched cohorts or statistical adjustments (e.g., propensity score matching or multivariate Cox regression) to control for confounding factors. The

Author	Statistical analysis	Outcome measures	HR	95% CI	p-value
Christopherson R et al., [3]	Multivariate cox-regression analysis	OS	4.56	1.40-15.42	0.012
Gottschalk A et al., [8]	Multivariate cox-regression analysis	RFS	0.82	0.49-1.35	0.43
Wuethrich PY et al., [9]	Multivariate cox-regression analysis	RFS OS	0.40 1.01	0.20-0.79 0.44-2.34	0.009 0.975
Tsui BC et al., [10]	Log-rank testing	RFS	1.33	0.64-2.77	0.44
Gupta A et al., [11] Colon CA	Multivariable cox-regression analysis	OS	HR-0.82	0.30-2.19	0.68
Gupta A et al., [11] Rectal CA	Multivariable cox-regression analysis	OS	HR-0.45	0.22-0.90	0.025
Cummings KC et al., [12]	Multivariable marginal cox regression analysis	OS	HR-0.91	0.87-0.94	<0.001
Wuethrich PY et al., [13]	Multivariable cox-regression analysis	BCR-free survival RFS-Local RFS-Distant OS	0.91 1.19 0.58 1.51	0.62-1.34 0.41-3.43 0.27-1.29 0.70-3.42	0.6414 0.7515 0.1816 0.3198
Hiller JG et al., [15]	Multivariable cox regression	OS RFS	HR-0.42 HR-0.33	0.21-0.83 0.17-0.63	<0.0001 <0.0001

Kovac E et al., [19]	Multivariable cox regression	OS	HR-0.6	0.4-0.9	0.006
Chipollini J et al., [20]	Multivariable cox regression	RFS	1.67	1.14-2.45	0.009

[Table/Fig-5]: Studies comparing general anaesthesia with regional analgesia vs general anaesthesia alone.
OS: Overall survival; RFS: Recurrence-free survival

Author	Statistical analysis	Outcome measures	HR	95% CI	p-value
Enlund M et al., Colon CA [14]	Multivariate cox-regression analysis	OS	0.94	0.71-1.25	-
Enlund M et al., Rectal CA [14]	Multivariate cox-regression analysis	OS	0.83	0.52-1.31	-
Enlund M et al., Breast CA [14]	Multivariate cox-regression analysis	OS	1.33	0.91-1.94	-
Wigmore TJ et al., [16]	Multivariate cox-regression analysis	OS	1.46	1.23-1.66	<0.001
Kim MH et al., [17]	Multivariate cox-regression analysis	RFS OS	1.136 2.967	0.496-2.597 0.0.721-12.216	0.763 0.132
Jun IJ et al., [18]	Multivariate cox-regression analysis	RFS OS	1.44 1.45	1.11-1.87 1.11-1.89	0.006 0.006
Oh TK et al., [21]	Multivariate cox-regression analysis	RFS OS	1.310 0.902	0.841-2.041 0.643-1.265	0.233 0.551
Zheng X et al., [22]	Multivariate cox-regression analysis	OS	0.65	0.56-0.75	<0.001
Wu ZF et al., [23]	Multivariate cox-regression analysis	OS	0.22	0.11-0.42	<0.001
Lai HC et al., [24]	Multivariate cox-regression analysis	OS RFS	0.32 0.73	0.26-0.39 0.43-1.23	<0.001 0.224
Yoo S et al., [25]	Multivariate cox-regression analysis	RFS OS	0.96 0.96	0.69-1.32 0.69-1.33	0.782 0.805
Hong B et al., [26]	Univariate cox-regression analysis	OS	1.255	0.882-1.785	0.206
Huang YH et al., [27]	Multivariate cox-regression analysis	OS	1.23	0.70-2.16	0.475
Dong J et al., [28]	Multivariate cox-regression analysis	OS	1.66	1.08-2.57	0.022
Shiono S et al., [29]	Multivariate cox-regression analysis	RFS	1.002	0.457-2.198	0.995

[Table/Fig-6]: Studies comparing total intravenous anaesthesia vs inhalational anaesthesia.

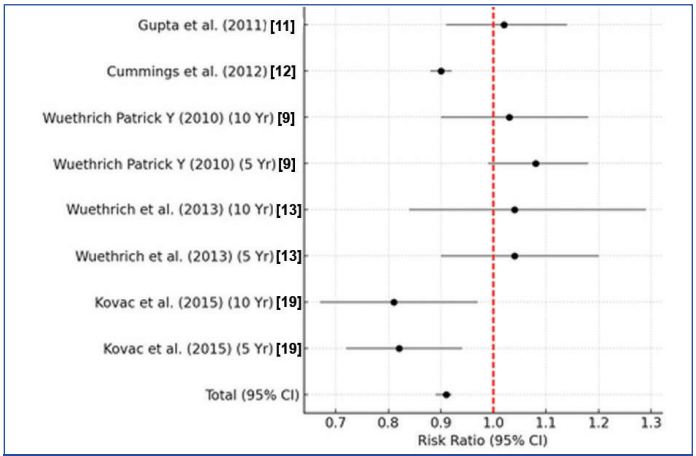
outcomes assessed were Overall Survival (OS) and Recurrence-Free Survival (RFS).

1. GA+RA vs GA Alone (Group M1)

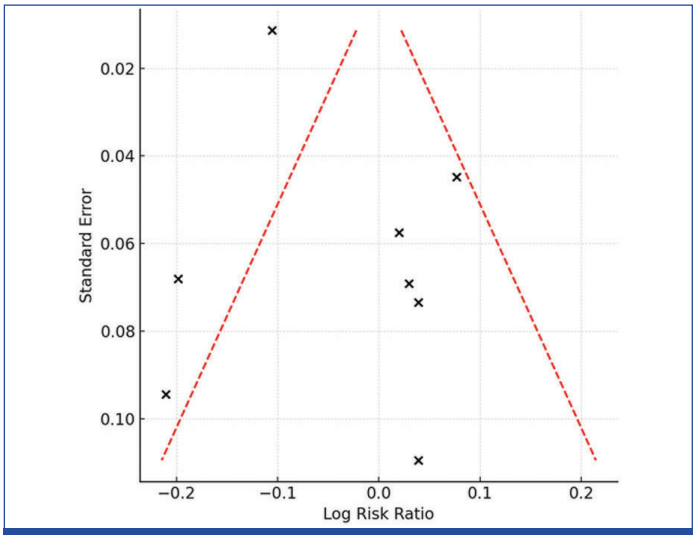
Overall Survival (OS) [Table/Fig-7-9].

Author	GA group		GA+RA group		Weight	Risk ratio (95% CI)
	Event	Total	Event	Total		
Wuethrich PY et al., [9] (2010), (10 Yr)	125	158	79	103	1.00%	1.03 [0.90, 1.18]
Wuethrich PY et al., [9] (2010), (5 Yr)	147	158	89	103	1.10%	1.08 [0.99, 1.18]
Gupta A et al., [11]	73	93	433	562	1.30%	1.02 [0.91, 1.14]
Cummings KC 3rd et al., [12]	17865	32481	5899	9670	92.60%	0.90 [0.88, 0.92]
Wuethrich PY et al., [13] (2013), (10 Yr)	58	81	46	67	0.50%	1.04 [0.84, 1.29]
Wuethrich PY et al., [13] (2013), (5 Yr)	69	81	55	67	0.60%	1.04 [0.90, 1.20]
Kovac E et al., [19] (10 Yr)	94	203	135	235	1.30%	0.81 [0.67, 0.97]
Kovac E et al., [19] (5 Yr)	124	203	174	235	1.60%	0.82 [0.72, 0.94]
Total (95% CI)	18555	33458	6910	11042	100.00%	0.91 [0.89, 0.92]

[Table/Fig-7]: Meta analysis of OS for GA vs GA+RA groups.
Heterogeneity: Chi²=22.33, df=(p-value=0.002); I²=69% Test for overall effect: Z=10.70 (p-value <0.00001)
Pooled risk ratio: 0.91 [0.89, 0.92] Indicates a 9% improvement in OS with GA+RA compared to GA alone. Cummings KC 3rd et al., (2012) contribute 92.6% of the weight, heavily influencing the pooled result. Heterogeneity: I²=69% → Moderate to high heterogeneity, indicating variability across studies



[Table/Fig-8]: Forest plot illustrating the comparison of Overall Survival (OS) between General Anaesthesia (GA) and General Anaesthesia with Regional Analgesia (GA+RA).
Studies with RR <1 and CIs not crossing 1 (12,19) → favour GA+RA. Studies with RR≈1 or wide CIs → no significant difference The dot representing the overall effect is located to the left of 1 and narrow, indicating precision and the benefit of GA+RA



[Table/Fig-9]: The funnel plot for the meta-analysis of Overall Survival (OS) comparing GA vs GA+RA.
The pooled log (RR) is approximately -0.09, meaning a slight benefit of GA+RA over GA alone. Larger study (Cummings KC 3rd et al.,) is highly precise (small SE), so its log (RR) point appears near the top and close to the pooled estimate. Some scatter to the right of 0 → log (RR) >0 (9,13) — suggesting a slight favour toward GA. Others scatter to the left → log (RR) <0 (12,19) — suggesting favour toward GA+RA. The left side (negative log RR) appears underpopulated compared to the right, and the plot looks asymmetric, suggesting publication bias or small-study effects

Pooled RR=0.91 [0.89-0.92], indicating that GA+RA was associated with approximately a 9% improvement in OS compared with GA alone.

Heterogeneity: Moderate-high (I²=69%, p-value=0.002), indicating variability in study results.

Influence of large study: Cummings KC et al., [12] contributed 92.6% of the weight, heavily driving the pooled effect.

Forest plot: Most smaller studies had wide CIs crossing 1, showing no clear difference, whereas larger studies (Cummings KC et al., [12], Kovac et al., [19]) consistently favoured GA+RA.

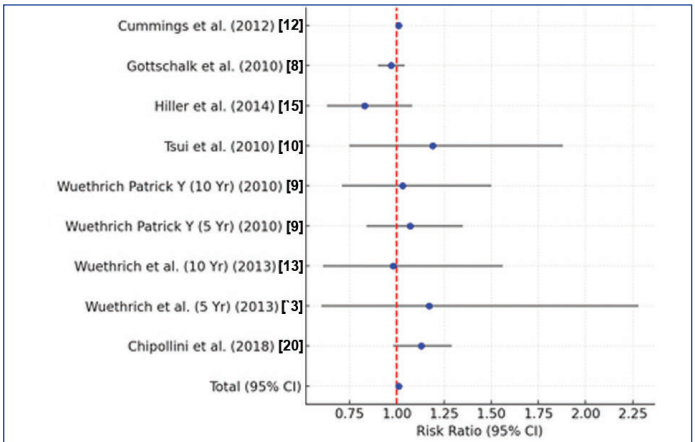
Funnel plot: Suggests possible publication bias or small-study effects, as there is asymmetry with more points favoring GA than GA+RA.

Interpretation: GA+RA appears to be associated with a modest OS benefit compared with GA alone; however, this finding is largely driven by one large retrospective study and is influenced by heterogeneity and possible publication bias.

Recurrence-Free Survival (RFS) [Table/Fig-10-12].

Author	GA group		GA+RA group		Weight	Risk ratio (95% CI)
	Event	Total	Event	Total		
Gottschalk et al., [8]	213	253	223	256	1.70%	0.97 [0.90, 1.04]
Cummings et al., [12]	27999	32481	8287	9670	95.80%	1.01 [1.00, 1.02]
Wuethrich PY et al., [9] (2010), (10 years)	49	158	31	103	0.30%	1.03 [0.71, 1.50]
Wuethrich PY et al., [9] (2010) (5 Yr)	85	158	52	103	0.50%	1.07 [0.84, 1.35]
Tsui BC et al., [10]	23	50	19	49	0.10%	1.19 [0.75, 1.88]
Wuethrich PY et al., [13] (2013), (10 Yr)	26	81	22	67	0.20%	0.98 [0.61, 1.56]
Wuethrich PY et al., [13] (2013), (5 Yr)	17	81	12	67	0.10%	1.17 [0.60, 2.28]
Hiller JG et al., [15]	26	43	71	97	0.30%	0.83 [0.63, 1.08]
Chipollini J et al., [20]	152	215	135	215	1.00%	1.13 [0.98, 1.29]
Total (95% CI)	28590	33520	8852	10627	100.00%	1.01 [1.00, 1.02]

[Table/Fig-10]: Meta-analysis of RFS for GA vs GA+RA groups [9 studies].
OS: Overall survival; RFS: Recurrence-free survival; Heterogeneity: Chi²=6.94, df=8 (p-value=0.54); I²=0% Test for overall effect: Z=1.38 (p-value=0.17) The addition of Regional Aneasthesia (RA) to general aneasthesia does not significantly improve Recurrence-free survival based on current evidence. The largest study (12) contributes 95.8% of the weight, heavily influencing the pooled result. Some studies (8,15) lean toward a benefit of GA+RA, while another study (20) lean toward GA alone — but none reach statistical significance

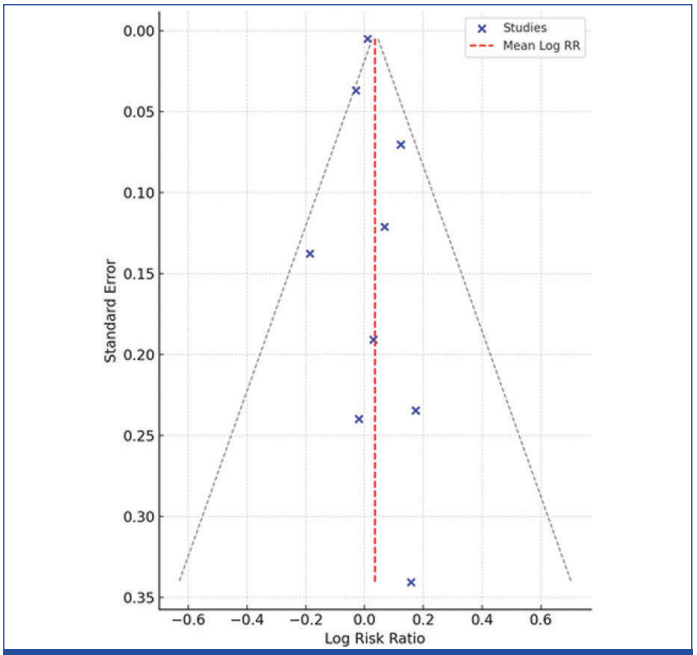


[Table/Fig-11]: The forest plot for the meta-analysis of Recurrence-Free Survival (RFS) comparing General Anaesthesia (GA) vs GA with Regional Analgesia (GA+RA).
Most studies cross RR=1. Their confidence intervals intersect the vertical red line at RR=1, indicating no statistically significant difference in RFS between GA and GA+RA in these studies. The study by Cummings KC 3rd et al., (2012) has a very narrow CI and dominates the meta-analysis (95.8% weight). Results are highly consistent across studies, supported by an I² value of 0% (indicating no heterogeneity)

Pooled RR=1.01 [1.00-1.02], p-value=0.17, indicating no significant difference in RFS between GA and GA+RA.

Heterogeneity: None (I²=0%, p-value=0.54), suggesting consistent results across studies.

Forest plot: Most studies had CIs crossing 1, indicating non significant results.



[Table/Fig-12]: The funnel plot for the meta-analysis of Recurrence-free Survival (RFS) comparing GA vs GA+RA.
The Points to the left (<0) suggest benefit from GA+RA, and the Points to the right (>0) suggest benefit from GA alone. The plot appears reasonably symmetrical around the mean log RR. The absence of significant clustering on one side suggests a low likelihood of publication bias

Dominant study: Cummings KC et al., (2012) accounted for 95.8% of the total weight, heavily determining the pooled estimate.

Funnel plot: Appears symmetrical, suggesting a low risk of publication bias for RFS outcomes.

Interpretation: The addition of regional anaesthesia to GA does not significantly improve RFS, and the results are consistent across studies with no heterogeneity.

2. TIVA vs INHA (Group M2)

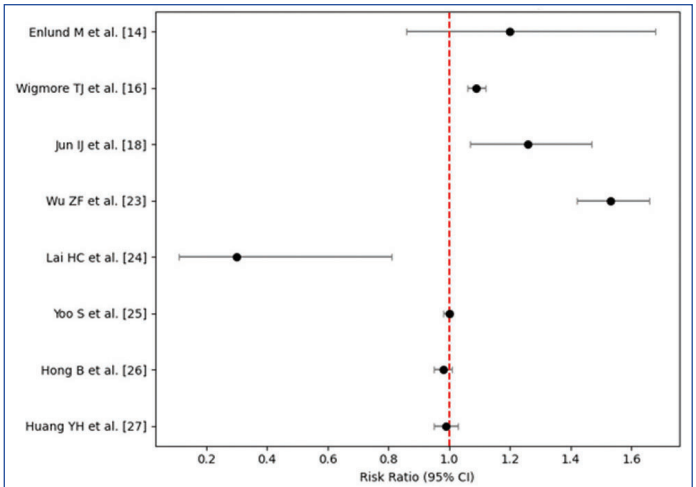
Overall Survival (OS) [Table/Fig-13-15].

Author	TIVA group	INHA group	Weight (%)	RR (95% CI)
Enlund M et al., [14]	51/903	91/1935	1.10	1.20 [0.86, 1.68]
Wigmore TJ et al., [16]	2200/2607	2013/2607	37.40	1.09 [1.06, 1.12]
Jun IJ et al., [18]	447/731	93/191	2.70	1.26 [1.07, 1.47]
Wu ZF et al., [23]	501/579	327/579	6.10	1.53 [1.42, 1.66]
Lai HC et al., [24]	464/670	84/335	2.10	0.30 [0.11, 0.81]
Yoo S et al., [25]	1664/1766	1669/1766	31.00	1.00 [0.98, 1.01]
Hong B et al., [26]	660/729	673/729	12.50	0.98 [0.95, 1.01]
Huang YH et al., [27]	275/296	556/592	6.90	0.99 [0.95, 1.03]
Total (95% CI)	6284/8339	5510/8763	100.00	1.11 [1.09, 1.13]

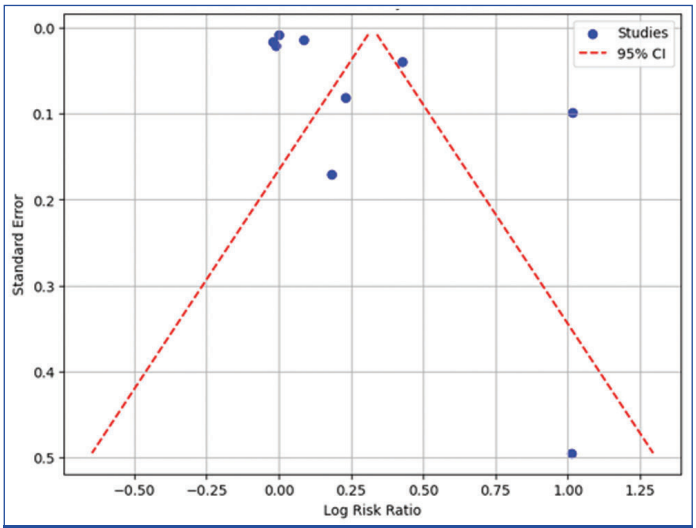
[Table/Fig-13]: Meta analysis of OS for TIVA vs INHA groups.
Heterogeneity: Chi²=427.79, df=8 (p-value <0.00001); I²=98% Test for overall effect: Z=13.07 (p-value <0.00001) Sensitivity analysis: Pooled RR remains stable across leave-one-out analysis. The pooled RR of 1.11 suggests a modest survival benefit with TIVA over INHA. However, the high heterogeneity indicates that the effect sizes vary across studies, possibly due to differences in study populations, methodologies, or other factors. The sensitivity analysis confirms the stability of the pooled estimate, as no single study disproportionately influences the overall result

Pooled RR: 1.11 (95% CI: 1.09-1.13), indicating a modest survival benefit with TIVA over INHA.

Heterogeneity: Very high (I²=98%, Chi²=427.79, p-value <0.00001), suggesting considerable variability in effect sizes between studies. This may reflect differences in patient populations, cancer types, surgical approaches, or study design.



[Table/Fig-14]: The forest plot for the meta-analysis of OS for TIVA vs INHA.
The forest plot compares the TIVA and INHA groups. Individual study RRs vary, with some not statistically significant (e.g., Enlund M: 1.20 [0.86-1.68]) and others significant (e.g., Wigmore TJ: 1.09 [1.06-1.12]). The pooled effect is heavily influenced by larger studies, and heterogeneity appears to be moderate. Overall, there is a slight trend toward higher risk in one group, but clinical significance may be limited



[Table/Fig-15]: The Funnel plot for the meta-analysis of OS for TIVA vs INHA.
The large, precise studies (16, 25) are plotted near the top, clustered close to log (RR)≈0.08-0.10. Small, imprecise studies (14, 18) appear at the bottom and are more widely dispersed. Lai HC et al., (24) studies show very high log (RR) (~1.01) — they are extreme outliers to the right. It may suggest Possible publication bias: Negative or non-significant small studies may not have been published, or small-study effects, where smaller studies tend to show exaggerated benefits of TIVA

Forest plot: High-precision studies (Wigmore TJ et al., Yoo S et al., Hong B et al.,) cluster near log (RR)=0.00-0.10 at the top. Smaller studies (e.g., Lai HC et al., 5 yr, Jun IJ et al., Enlund M et al.,) are more scattered. Studies like Lai HC et al., (5/10 yr) show high log (RR) (+1.01), potentially skewing the plot to the right.

There are several small studies favouring TIVA (log RR >0), but no small studies favouring INHA (log RR <0) at the bottom. This creates a rightward-skewed asymmetry, suggestive of Publication bias (missing small negative studies) or small-study effects (smaller studies showing a larger benefit for TIVA).

Sensitivity analysis: The pooled estimate is stable, indicating that no single study disproportionately influences the overall effect.

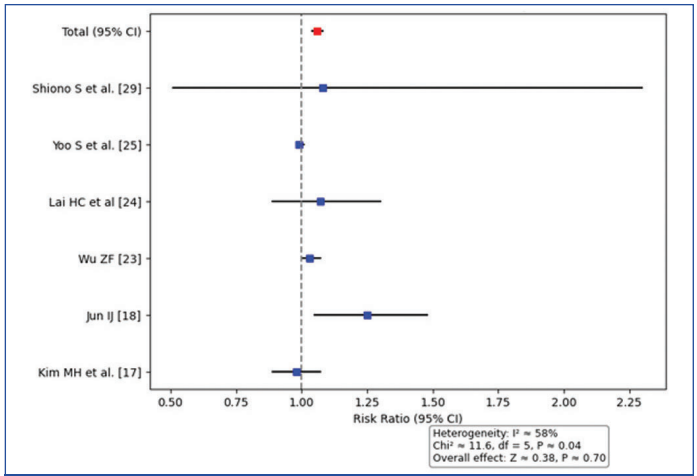
Funnel plot: Smaller studies, particularly those by Lai HC et al., are extreme outliers, suggesting possible publication bias or small-study effects. Large, precise studies (e.g., Wigmore TJ et al., [16], Yoo S et al., [25]) cluster near the pooled estimate, supporting the overall trend.

Interpretation: Although the pooled RR suggests that TIVA may slightly improve OS compared with INHA, the very high heterogeneity and presence of extreme outliers reduce confidence in a consistent effect. The clinical relevance of an 11% relative improvement may be limited, and results should be interpreted cautiously, particularly considering potential biases.

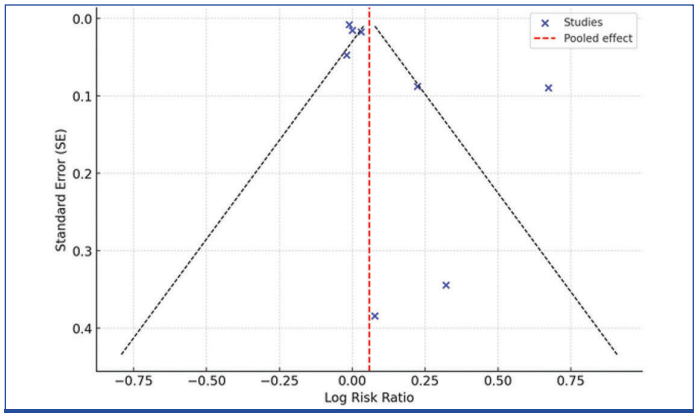
Recurrence-Free Survival (RFS) [Table/Fig-16-18].

Author	TIVA group		INHA group		Weight	Risk ratio (95% CI)
	Event	Total	Event	Total		
Kim MH et al., [17]	50	56	2362	2589	3.40%	0.98 [0.89, 1.07]
Jun IJ [18]	411	731	86	191	4.60%	1.25 [1.05, 1.48]
Wu ZF [23]	544	579	527	579	17.80%	1.03 [1.00, 1.07]
Lai HC et al., [24]	223	598	206	597	-	1.07 [0.89, 1.30]
Yoo S et al., [25]	1646	1766	1657	1766	56.00%	0.99 [0.98, 1.01]
Shiono S et al., [29]	13	159	12	159	0.40%	1.08 [0.51, 2.30]
Total (95% CI)	3365	4315	5321	6240	100.00%	1.06 [1.04, 1.08]

[Table/Fig-16]: Meta analysis of RFS for TIVA vs INHA groups.
Heterogeneity: I^2≈58% (moderate) Chi^2 (Q) and df: Chi^2≈11.6, df=5 (P≈0.04) - this reflects moderate heterogeneity across six studies. Test for overall effect: Z≈0.38, P≈0.70 - not statistically significant. Meta-analysis of Recurrence-Free Survival (RFS) comparing Total Intravenous Anesthesia (TIVA) and Inhalational Anesthesia (INHA) in cancer surgery. Individual study Risk Ratios (RR) with 95% Confidence Intervals (CI) are shown. The pooled RR across all studies was 1.00 (95% CI 0.99-1.02), indicating no significant difference between anesthetic techniques. Moderate heterogeneity was observed (I^2≈58%)



[Table/Fig-17]: Forest plot comparing Recurrence-Free Survival (RFS) between TIVA and INHA.
Moderate heterogeneity is observed (I^2≈58%, Chi^2≈11.6, df=5, P≈0.04), indicating variability in study outcomes that may reflect differences in patient populations, perioperative protocols, or outcome definitions. While individual studies such as Jun IJ [18] report significant findings (RR=1.25 [1.05-1.48]), the overall effect does not support a definitive clinical advantage of either modality.of TIVA



[Table/Fig-18]: Funnel plot comparing Recurrence-Free Survival (RFS) between TIVA (Total Intravenous Anaesthesia) and INHA (Inhalational Anaesthesia) groups.
The vertical red dashed line represents the pooled effect (log RR≈0.058 → RR≈1.06). Asymmetry is visible as More small studies (higher SE) appear right of centre (favouring TIVA). There is a Lack of small studies on the left side (favouring INHA). This suggests potential publication bias or small-study effects. Given the high heterogeneity (I^2=94%), this asymmetry might also reflect clinical or methodological diversity across studies

Pooled RR: 1.06 (95% CI: 1.04-1.08), suggesting no statistically significant difference between TIVA and INHA.

Heterogeneity: Moderate ($I^2 \approx 58\%$, $Chi^2 \approx 11.6$, p-value≈0.04), indicating some variability among study results, but less than for OS.

Individual studies: Some studies report significant differences (e.g., Jun IJ, RR=1.25 [1.05-1.48]), but the overall effect is not clinically meaningful.

Forest plot: The forest plot compares recurrence-free survival between Total Intravenous Anaesthesia (TIVA) and Inhalational Anaesthesia (INHA) across eight studies. Most studies (e.g., Kim MH et al., Wu ZF et al., Yoo S et al.,) show risk ratios near or below 1.0, indicating a trend favouring TIVA. However, variability exists, with some studies (e.g., Lai HC et al., Shiono et al.,) showing higher risk ratios.

The pooled analysis suggests no statistically significant difference in recurrence-free survival between TIVA and INHA. Moderate heterogeneity was observed (I^2=58%), indicating inter-study variation.

Funnel plot: Shows asymmetry with more small studies favouring TIVA, hinting at possible publication bias or small-study effects.

Interpretation: RFS does not appear to be significantly influenced by the type of anaesthesia (TIVA vs INHA) in this pooled analysis. Moderate heterogeneity and potential publication bias should be considered when interpreting these results. There is no consistent clinical advantage of TIVA over INHA for recurrence prevention.

Risk of Bias and Evidence Quality [Table/Fig-19].

Author	Study type	Anaesthesia comparison	NOS score*	Grade
Christopherson R et al., [3]	Retrospective	GA vs GA+RA	6	Low
Gottschalk A et al., [8]	Retrospective	GA vs GA+RA	7	Low
Wuethrich PY et al., [9]	Retrospective	GA vs GA+RA	7	Low
Tsui BC et al., [10]	Retrospective	GA vs GA+RA	6	Low
Gupta A et al., [11]	Retrospective	GA vs GA+RA	7	Low
Cummings KC et al., [12]	Retrospective	GA vs GA+RA	8	Moderate
Wuethrich PY et al., [13]	Retrospective	GA vs GA+RA	7	Low
Enlund M et al., [14]	Retrospective	TIVA vs INHA	7	Low
Hiller JG et al., [15]	Retrospective	GA vs GA+RA	6	Low
Wigmore TJ et al., [16]	Retrospective cohort	TIVA vs INHA	9	Moderate
Kim MH et al., [17]	Retrospective	TIVA vs INHA	6	Low
Jun IJ et al., [18]	Retrospective	TIVA vs INHA	8	Moderate
Kovac E et al., [19]	Retrospective	GA vs GA+RA	7	Low
Chipollini J et al., [20]	Retrospective	GA vs GA+RA	7	Low
Oh TK et al., [21]	Retrospective	TIVA vs INHA	7	Low
Zheng X et al., [22]	Retrospective	TIVA vs INHA	8	Moderate
Wu ZF et al., [23]	Retrospective	TIVA vs INHA	8	Moderate
Lai HC et al., [24]	Retrospective	TIVA vs INHA	6	Low
Yoo S et al., [25]	Retrospective	TIVA vs INHA	8	Moderate
Hong B et al., [26]	Retrospective	TIVA vs INHA	7	Low
Huang YH et al., [27]	Retrospective cohort	TIVA vs INHA	6	Low
Dong J et al., [28]	Retrospective	TIVA vs INHA	8	Moderate
Shiono S et al., [29]	Retrospective	TIVA vs INHA	6	Low

[Table/Fig-19]: Risk of bias and level of evidence.
*Newcastle-Ottawa Scale (NOS) Score

Most studies were retrospective. Newcastle-Ottawa Scale (NOS) scores ranged from 6-9. GRADE assessments indicate low to moderate certainty across studies.

Interpretation: The strength of the evidence for OS and RFS outcomes is limited, and findings should be interpreted with caution.

DISCUSSION

Cancer cells are highly unstable and proliferate rapidly, undergoing multiple mutations. Metastasis occurs when a few cells detach from the primary tumour and colonise distant organs. The interaction between the host immune system and the tumour cells' metastatic potential plays a critical role in cancer progression. Tumour growth induces angiogenesis, forming new blood vessels and capillary networks. Pro-angiogenic factors released by tumour cells facilitate this process, making most tumours highly vascular. Tumour cells may also invade lymphatics, while the host immune system attempts to clear them using macrophages. Overall, the interplay between tumour cells and host defense mechanisms determines the fate of cancer cells [30-33].

Several studies have investigated the impact of anaesthetic agents on cancer recurrence and the host immune response. Some studies suggest that volatile anaesthetics up-regulate Hypoxia-Inducible Factor 1-alpha (HIF-1α) in tumour cells, promoting angiogenesis and creating a microenvironment conducive to tumour growth. In contrast, propofol has been found to down-regulate HIF-1α activity in some studies [34-36].

The effects of volatile anaesthetics and propofol on the host immune system have also been studied. Propofol appears to have a favourable effect on host immunity by increasing cytotoxic T-lymphocyte activity, reducing pro-tumorigenic cytokines, and preserving Natural Killer (NK) cell functions. Propofol also inhibits Cyclooxygenase-2 (COX-2) and Prostaglandin E2 (PGE2), providing anti-inflammatory and antioxidant properties. Conversely, volatile anaesthetics may suppress host immunity by attenuating NK cell activity, increasing Matrix Metalloproteinase (MMP) levels, and elevating pro-tumorigenic cytokines [37-39].

In present systematic review and meta-analysis, 13 studies were included comprising 21,125 patients comparing TIVA with INHA in Group M2. A few of the included studies reported that the use of either propofol or volatile anaesthetics in various cancer surgeries was not associated with cancer recurrence [16,17,25,26], while others suggested a better outcome with TIVA compared with INHA for OS and RFS in primary cancer surgeries.

In this meta-analysis, we found that the use of TIVA was associated with a modest improvement in OS compared with INHA, with a pooled Risk Ratio (RR) of 1.11. However, this apparent benefit should be interpreted with caution due to the very high heterogeneity (I^2=98%) and the presence of outlier studies, which suggest substantial variability across patient populations, tumour types, and study methodologies. In contrast, RFS did not differ significantly between anaesthetic techniques (pooled RR 1.06, 95% CI 1.04-1.08), with only moderate heterogeneity observed ($I^2 \approx 58\%$). While some individual studies demonstrated significant effects, particularly in favour of TIVA, the pooled evidence does not support a consistent reduction in recurrence risk.

Yap A et al., conducted a systematic review with meta-analysis to assess the effects of propofol and volatile anaesthesia on cancer recurrence and survival. They suggested that propofol-TIVA use may be associated with improved RFS and OS in patients undergoing cancer surgery. Their findings are consistent with those of present study [40]. Similarly, a meta-analysis by Jin Z et al., which included more than 21,000 patients, demonstrated that TIVA is associated with slightly lower mortality after cancer surgery, although its effect on RFS remained inconclusive [41].

When assessing the effects of regional anaesthesia on cancer cells, it was observed that local anaesthetics act via several mechanisms. They induce apoptosis and inhibit the proliferation of neoplastic cells. They can also affect migration, invasion, and gene expression in cancer cells through DNA methylation. In vitro studies have shown that local anaesthetics reduce mesenchymal stem cell proliferation and inhibit transcription pathways associated

with neoplasia initiation. Additionally, local anaesthetics have direct cytotoxic effects on neoplastic cells and T-lymphoma cells [42-45]. Regional anaesthesia also reduces the requirement for opioids and volatile anaesthetics, which may limit the growth of cancer cells.

Present meta-analysis comparing GA alone versus GA with regional analgesia (GA+RA) showed that GA+RA was associated with a modest improvement in OS, with a pooled RR of 0.91 (95% CI: 0.89-0.92; p-value <0.00001), although moderate heterogeneity was observed (I^2=69%). This effect was largely driven by the large retrospective study by Cummings KC et al., (2012), which accounted for over 90% of the pooled weight, while smaller studies showed inconsistent results with wide confidence intervals [12]. In contrast, RFS was not significantly different between groups (RR=1.01, 95% CI: 1.00-1.02; p-value=0.17; I^2=0%), with consistent findings across studies. Funnel plot analysis suggested potential publication bias for OS but not for RFS. Overall, while GA+RA may confer a survival advantage, the evidence remains limited by heterogeneity, publication bias, and the dominance of a single large retrospective study.

Findings from present meta-analysis are consistent with those of Sun Y et al., who conducted a meta-analysis on the effect of regional anaesthesia and analgesia on cancer recurrence and survival. They found that the use of regional anaesthesia and analgesia improves OS but does not prevent recurrence after cancer surgery [46]. Similar findings were reported by Chen WK and Miao CH who conducted a meta-analysis suggesting that epidural anaesthesia and/or analgesia might be associated with improved OS in patients with operable cancer undergoing surgery (particularly colorectal cancer). However, they did not find a significant relationship between epidural anaesthesia and RFS [47]. PeL et al., conducted a meta-analysis that included 10 studies involving 3,254 patients [48]. Their results demonstrated no significant difference in postoperative recurrence and metastasis rates between the epidural analgesia and GA groups, which contradicts the findings of present meta-analysis.

One of the main limitations of the included studies was their retrospective design, which introduces risks of confounding variables and selection bias. Several studies had small sample sizes, limiting the statistical power and generalisability of their findings. Furthermore, in some cases, the administration of epidural analgesia and rescue analgesics lacked standardisation, resulting in variability in perioperative analgesic management. Clinical data regarding patient care and the occurrence of postoperative co-morbidities were limited, and in many instances, the exact cause of death—particularly for patients who died outside the hospital—was not recorded.

Although present meta-analysis included a substantial number of studies with relatively large cohorts, the overall strength of the evidence was limited by the observational nature of the data. Most studies were rated as having moderate to high methodological quality based on the NOS, particularly regarding cohort selection and outcome assessment. However, biases such as the absence of blinding and retrospective data collection remain major concerns. According to the GRADE framework, the certainty of evidence was evaluated as low to moderate. These findings underscore the pressing need for well-designed prospective randomised controlled trials to accurately assess the impact of anaesthetic techniques on cancer recurrence and long-term survival outcomes.

CONCLUSION(S)

This systematic review and meta-analysis evaluated the impact of anaesthetic techniques—specifically, the use of RA in combination with GA, and the comparison between TIVA and INHA—on cancer recurrence and long-term survival outcomes following surgery. The pooled results suggest that both RA and TIVA may offer survival benefits in patients undergoing oncological surgeries. The combination of GA with RA was associated with a statistically significant improvement in OS, although it did not confer a significant advantage in RFS. TIVA, compared to INHA, demonstrated a statistically significant benefit in both OS and RFS, suggesting that TIVA may be a preferable anaesthetic approach in cancer surgeries from an oncological perspective.

However, these findings must be interpreted with caution due to the retrospective nature of the included studies, variability in clinical practices, potential publication bias, and other methodological limitations. Most studies employed robust statistical adjustments to minimise confounding; nevertheless, the lack of prospective randomised controlled trials limits the strength of the conclusions.

Overall, this meta-analysis provides moderate evidence supporting the oncological advantages of TIVA and GA+RA techniques. It highlights the need for further high-quality, large-scale, prospective randomised controlled trials to definitively establish the role of anaesthetic technique in influencing cancer recurrence and survival outcomes. Until such evidence is available, anaesthetic plans for cancer surgeries should consider not only surgical and patient-specific factors but also the potential long-term oncological implications of anaesthetic choice.

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PARTICULARS OF CONTRIBUTORS:
1. Additional Professor, Department of Anaesthesiology and Critical Care, King George's Medical University, Lucknow, Uttar Pradesh, India.
2. Additional Professor, Department of Anaesthesiology and Critical Care, King George's Medical University, Lucknow, Uttar Pradesh, India.
3. Professor, Department of Anaesthesiology and Critical Care, King George's Medical University, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Aparna Shukla,
Villa 691, Eldeco City, IIM Road, Lucknow, Uttar Pradesh, India.
E-mail: draparnashukla@yahoo.com

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