Intravenous Anesthesia Offers a Better Overall Survival Outcomes Than Inhalation Anesthesia of Malignant Tumor After Surgery: A Meta-Analysis

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Abbreviations:
TIVA: Total Intravenous Anesthesia; INVA: Inhalation Anesthesia; Exp: Experiment; Con: Control; ASA: American Society of Anesthesiologists; HGG: High-Grade Glioma; RARP: Robot-Assisted Radical Postatectomy; NSCLC: Non-Small Cell Lung Cancer Surgery; ICC: Hepatocellular Carcinoma; MRM: Modified Radical Mastectomy; BCS: Breast Conserving Surgery; BMI: Body Mass Index; Min: Minutes; Mon: Months; MFT: Median Follow-up Time; OS: Overall Survival; RFS: Recurrence - Free Survival

Keywords:
Intravenous anesthesia; Inhalation anesthesia; Malignant tumor; Meta-analysis

Author Contributions:
Qiu S, Chen Z and Liu H. These authors have contributed equally to this article.

1. Abstract
1.1. Background and Objectives: Previous studies have shown that the anesthesia type during surgery would affect the long-term oncological outcomes of malignant tumor. Intravenous anesthesia (TIVA) and inhalation anesthesia (INVA) are two different methods of maintenance anesthesia, but which one offers a better prognosis effect for malignant diseases has not been fully confirmed. Therefore, the aim of this meta-analysis was to provide a further evidence that whether the TIVA would reduce recurrence and improve survival relative to inhaled INVA after surgery.

1.2. Methods: We have fully searched the online database and the reference list of each potential included study. We used Stata 12.0 to analyze HR and CI values. We used Review Manager 5.3 to evaluate the quality of the studies. The recurrence rate and survival rate after operation were pooled. The Mantel-Haenszel random effects model was used to calculate the combined hazard ratios (HR) and its 95% confidence intervals (CI) for recurrence-free rate (RFS) and over survival (OS).

1.3. Results: A total of 11 studies were included, with the types of colon cancer, high-grade glioma (HGG), hepatocellular carcino-
FE et al showed that opioids promote proliferation and invasion and promoted the response of anti-tumor NKCC and cytokines [7]. Dong H et al. General/epidural anesthetics dominate more effectively, inhibit the stress response and minimize immune dysfunction [6]. Anesthesia procedure during malignant tumor surgery is always being a controversial issue and, in general, may affect endocrine function, immune function, stress response and prognosis of tumor surgery [3].

A large number of studies have shown that anesthesia technology was related to immunological and inflammatory pathways that activate tumor growth related factors, and it is highly likely to affect the prognosis of surgery through these mechanisms [1]. So more and more people begin to pay attention to the different anesthesia methods and whether the maintenance of anesthesia during the operation will affect the recurrence and survival rate after surgery, so a considerable number of studies have been devoted to this aspect. In recent years, many studies including cohort studies, systematic reviews and meta-analysis as well as some mechanism studies have investigated the effect of anesthetic technique on tumor prognosis (recurrence and survival) [4]. Studies have shown that epidural anesthesia/analgesia can reduce the stress response of esophageal cancer patients, improve postoperative recovery and improve survival rate [5], and epidural anesthesia can inhibit the 2-5a-dominance more effectively, inhibit the stress response and minimize immune dysfunction [6]. Dong H et al General/epidural anesthesia significantly increased NKCC, il-10 and decreased il-1, and promoted the response of anti-tumor NKCC and cytokines [7]. Opioid use during anesthesia also affects tumor prognosis. Lennon FE et al showed that opioids promote proliferation and invasion by activating l receptors on the surface of NSCLC and breast cancer cells [8]. In addition, Pei et al have performed a meta-analysis demonstrated that general-epidural anesthesia (EGA) may be associated with improved outcomes in operable prostate cancer patients and cancer patients who were followed for less than or equal to two years [9]. Sun et al. have performed meta-analysis certified the perioperative regional anesthesia (RA) use was associated with improved over survival [10]. Holler, J. P. et al. made a meta-analysis suggested epidural analgesia (PDA) under general anesthesia has potential benefits for long-term survival after colorectal cancer surgery [11]. Weng et al. also performed a meta-analysis to research the effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery [12]. However, in recently, in vitro and in vivo studies have shown that propofol can relatively reduce tumor cell metastasis [13], and total intravenous (TIVA) and inhaled anesthesia (INVA) may also be associated with survival after tumor surgery. And a number of cohort studies have been conducted to study the effects of intravenous anesthesia (TIVA) and inhalation anesthesia (INVA) on postoperative prognosis of tumors with different conclusions recently. But the results in each study were inconsistent. Yap, A.et al. and Zhaosheng Jin et al. studied A comprehensive study to evaluated the effect of TIVA and INVA on postoperative survival prognosis of tumors, but the results were contradictory [14, 15]. And there was not enough statistical significance to indicate whether TIVA or INVA was better for tumor prognosis.

Therefore, in attempt to obtain a more accurate and reliable conclusion about the TIVA and INVA which can improve the long-term survival and reduce recurrence, we have conducted this relevant meta-analysis.

3. Methods

3.1. Information Source and Literature Search

In order to testify the areas in which Anesthesia method (TIVA or INVA) may have a better benefit on survival after cancer operation, we performed a meta-analysis. We searched on PubMed database for the keywords (anesthesia, Neoplasms and survival, including their subject words and random words). In addition to searched on PubMed database, we also review the references from the included the studies to ensure no any other related studies had been overlooked. Two authors worked independently and used a same standard form to review studies and extract data.

An author then collected the basic features and HR values (TIVA vs INVA) and confidence intervals (CI) of each included literature from the articles. Some studies in order to conform to TIVA vs INVA, we recorded 1/HR, while some studies (Wu et al [16], Yan et al [17], Lee et al [18], Stefan J.Grau et al[19], Yan et al.[20]) only had survival curves, we extracted the HR value and its CI by Engauge Digitizer more than three times for each data to take the average. Finally, the two authors checked all the information to ensure the accuracy. The outcomes of this meta-analysis were overall...
survival and recurrence-free survival. The inclusion criteria of the selected studies were as follow:

1) Studies with patients undergoing tumor-related surgery;
2) Interventions studies comparing the use of TIVA or INVA;
3) Studies of long-term survival after surgery.

The exclusion criteria were as follow:

1) Interventions studies not about the TIVA and INVA
2) Studies were Reviews and meta-analysis
3) The results not about recurrence or survival
4) Studies were experimental studies
5) Studies lacks relevant data

3.2. Studies Quality Assessment

The quality of studies was evaluated using NOS (Newcastle-Ottawa quality assessment scale) which includes 8 items with covers three aspects: selection, comparability, outcomes. Add NOS items to Reman5.3 for evaluation, and qualities of included studies were assessed by two authors independently. Every evaluation is supported by the original text. And we classified as unclear risks those who were followed for less than 3 years, and all studies were high quality.

3.3. Statistical Analysis

In this meta-analysis, two authors collected the information carefully and the software of analyzing is Stata, version 12.0. Risk estimates were extracted with CI and P value. Risk is the ratio of two risks (Exp/Ctr) within a given time. It not only considers the existence of endpoint events, but also takes into account the time taken to reach the endpoint and truncated data, which plays a decisive role in evaluating the result. An HR > 1, indicates high risk of exposure group, HR < 1, indicates low risk of exposure group, HR = 1, it is no distinction in two groups. Confidence interval (CI) refers to the estimation interval of total parameters constructed by sample statistics, and in statistics, the CI of a probability sample is an estimate of an overall parameter of the sample. The Mantel-Haenszel random effects model was used to calculate the combined hazard ratios (HR) and its 95% confidence intervals (CI) for recurrence-free rate (RFS) and over survival (OS).

4. Result

4.1. Inclusion of Studies

After search in Pubmed, 1163 related articles were searched out. After the records excluded for title and abstracts reviews, there were have 24 full-text articles for eligibility but then because of 811 of studies are not about the TIVA and INVA on survival and recurrence and 24 of studies are reviews and meta-analysis and 19 are not for recurrence or survival and 11 of studies were experimental studies and 274 are others.3 of study have not relevant data, we deleted them. Eventually, there were 19 retrospective studies and 2 randomized controlled trial that met the inclusion criteria were considered for meta-analysis. (Figure 1) illustrates the literature search methodology.

4.2. Basic Characteristics of Studies

These studies were published from 2014 to 2020, and all of these are high quality, including 10286 cases in the Intravenous anesthesia (TIVA) group and 13666 cases in the Inhalation anesthesia (INVA) group which from China, Korea, Germany, Sweden and London. The types of cancer in these studies include high-grade glioma (HGG), breast cancer, Prostate cancer, colon cancer, intrahepatic cholangiocarcinoma, gastric cancer, non-small cell lung cancer surgery (NSCLC), esophageal cancer, hepatocellular carcinoma (HCC), rectal cancer. Overall survival (OS) and the recurrence-free survival (RFS) were used as the criteria to evaluate the prognosis of TIVA and INVA for different tumor surgery, and all the 18 studies analyzed the effects of anesthesia and OS, and 16 studies analyzed the effects of anesthesia and RFS. The basic characteristics of the studies design and content showed in (Table 1, Table 2).
<table>
<thead>
<tr>
<th>Author</th>
<th>Publication</th>
<th>Year</th>
<th>Type of study</th>
<th>Country</th>
<th>Tumor</th>
<th>Surgery types</th>
<th>ASA/I&amp;II</th>
<th>Treatment</th>
</tr>
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<td>PLOS ONE</td>
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<td>retrospective</td>
<td>China</td>
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<td>Robot-assisted radical prostatectomy</td>
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<td>propofol, desflurane</td>
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<td>Medical Principles and Practice</td>
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<td>retrospective</td>
<td>Korea</td>
<td>HCC</td>
<td>Laparoscopic hepatic resection</td>
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<td>propofol, desflurane</td>
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<tr>
<td>Stefan J.Grau et al.(19)</td>
<td>Scientific Reports</td>
<td>2020</td>
<td>retrospective</td>
<td>Germany</td>
<td>Glioblastoma</td>
<td>Resection of supratentorial primary glioblastoma</td>
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<td>propofol, thiopental, isoflurane, desflurane or sevoflurane</td>
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<tr>
<td>Na Young Kim et al.(23)</td>
<td>Int. J. Med. Sci.</td>
<td>2020</td>
<td>retrospective randomized</td>
<td>Korea</td>
<td>Prostate cancer</td>
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<td>propofol/ remifentanil, sevoflurane/ propofol/ remifentanil</td>
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<td>retrospective</td>
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<td>Elective heptectomy surgery</td>
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<td>propofol, desflurane</td>
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<td>BMC Anesthesiology</td>
<td>2019</td>
<td>retrospective</td>
<td>Korea</td>
<td>Gastric, lung, liver, colon or breast cancer</td>
<td>Resection for gastric, lung, liver, colon or breast cancer surgery</td>
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<td>Remifentanil with propofol, desflurane, sevoflurane, or isoflurane</td>
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<td>retrospective</td>
<td>Taiwan</td>
<td>Intrahepatic cholangiocarcinoma</td>
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<td>2019</td>
<td>retrospective</td>
<td>China</td>
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<td>HGG tumor resection</td>
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<td>retrospective</td>
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<td>2018</td>
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<td>Korea</td>
<td>NSCLC</td>
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<td>OncoTargets and Therapy</td>
<td>2018</td>
<td>retrospective</td>
<td>China</td>
<td>Gastric cancer</td>
<td>Gastric cancer resection</td>
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<td>Propofol, Sevoflurane</td>
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<tr>
<td>Yan et al.</td>
<td>BMC Anesthesiology</td>
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<td>Prospective</td>
<td>China</td>
<td>Breast cancer</td>
<td>MRM, BCS</td>
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<td>Propofol, Sevoflurane</td>
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<tr>
<td>Kim et al.(33)</td>
<td>Oncotarget</td>
<td>2017</td>
<td>retrospective</td>
<td>Korea</td>
<td>Breast cancer</td>
<td>Breast-conserving, Mastectomy</td>
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<td>Propofol, Sevoflurane, Barbiturate, Isoflurane, Enflurane</td>
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<td>Jun et al.(34)</td>
<td>Scientific reports</td>
<td>2017</td>
<td>retrospective</td>
<td>Korea</td>
<td>Esophageal cancer</td>
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<td>retrospective</td>
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<td>retrospective</td>
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<td>2016</td>
<td>retrospective</td>
<td>Korea</td>
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<td>MRM</td>
<td>164(94.8)</td>
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<td>M. Enlund et al.1(36)</td>
<td>Upsala Journal of Medical Sciences</td>
<td>2014</td>
<td>retrospective</td>
<td>Sweden</td>
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<td>Colon cancer surgery</td>
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<td>2014</td>
<td>retrospective</td>
<td>Västerås</td>
<td>Rectal cancer</td>
<td>Rectal cancer surgery</td>
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Exp, Experiment; Con, Control; ASA, American Society of Anesthesiologists; HGG, high-grade glioma; TIVA, Total intravenous anesthesia; INVA, Inhalation anesthesia; RARP, Robot-assisted radical prostatectomy; NSCLC, non-small cell lung cancer surgery; HCC, hepatoeellular carcinoma; MRM, modified radical mastectomy; BCS, breast conserving surgery;
Table 2: Basic characteristics of studies

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<th>Exp</th>
<th>Con</th>
<th>Exp</th>
<th>Con</th>
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<th>Exp</th>
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<td>Medical Principles and Practice</td>
<td>2020</td>
<td>121</td>
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<td>30(21.7)</td>
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<tr>
<td>Stefan J.Grau et al.</td>
<td>Scientific Reports</td>
<td>2020</td>
<td>79</td>
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<td>Oh et al(31)</td>
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<td>2017</td>
<td>56</td>
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<td>731</td>
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<td>Korean Journal of Anesthesiology</td>
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BMI, body mass index; Min, Minutes; Mon, Months; MFT, Median follow-up time; Exp, Experiment; Con, Control; OS, Overall survival; RFS, Recurrence - free survival

4.3. Outcome of Meta-Analysis with Overall Survival and Recurrence-Free Survival

AS showed in (Figure 2), 18 studies were all used to analysis the overall survival (OS) of the prognosis of TIVA and INVA for different tumor surgery in meta-analysis. The weighted HR for overall survival was 0.73, 95%CI (0.60-0.89), and it is in favor of TIVA, p= 0.02(I-Squared=86.1%). The result of this meta-analysis showed the TIVA benefits the overall survival (OS) relative to the INVA. Despite some trials showing the result of the INVA is in the favor of overall survival (OS). As for Recurrence free survival (RFS), the weighted HR was 0.76, 95%CI (0.58-0.98), and it is benefit in TIVA, p= 0.036(I-Squared=77.7%) (Figure 3).

4.4. The Outcome of Subgroup Analysis

4.4.1. Subgroup Analysis of Tumor: Subgroup analysis of different tumor (Breast Cancer, glioblastoma, liver cancer, Gastrointestinal Cancer, Other) of intravenous anesthesia (TIVA) compared to inhalation anesthesia (INVA) in overall survival, it showed that it was not statistically significant for the breast Cancer, and the HR was 0.97 (0.76, 1.25), P=0.815. But it showed that TIVA was better than INVA for gastrointestinal Cancer, HR was 0.62(0.43, 0.89), P=0.01. The TIVA showed the better recurrence - free survival in the gastrointestinal cancer HR=0.72, (0.57-0.91), P=0.006. But for the other cancers, survival was not statistically significant between the two anesthesia techniques (Figure 4).
Figure 2: Forest plot of overall survival: intravenous analgesia (TIVA) ± inhalation anesthesia (INVA). All studies had OR estimate obtained from a matched analysis, and left is in favor of TIVA, but right is in favor of INVA.

Figure 3: Forest plot of recurrence-free survival: intravenous anesthesia (TIVA) ± inhalation anesthesia (INVA). All studies had RFS estimate obtained from a matched analysis, and left is in favor of TIVA, but right is in favor of INVA.

Figure 4: Subgroup analysis of different tumor of TIVA compared to INVA in overall survival. (A) and in recurrence-free survival (B). Left is in favor of TIVA, but right is in favor of INVA.
4.4.2. Subgroup Analysis of Blood Transfusion: Blood transfusion constitutes an independent risk factor for the prognosis of cancer (20). Subgroup analysis of different blood transfusion percentage of TIVA compared INVA in overall survival, we found the TIVA had a better overall survival and recurrence-free survival than INVA when transfusion > 30% of people included in the study (HR=0.60, 95%CI 0.45-0.82, P=0.001), and (HR=0.24, 95%CI 0.16-0.35, P<0.001). However, when transfusion < 30% of people included in the study, it was not statistically significant in the two groups (Figure 5).

4.4.3. Publication Bias and Quality of Included Studies: We performed sensitivity analysis about the clinical trial. 2 anesthesia methods for 23952 tumor patients were included for analysis. The results were stable and were similar to main analysis. Begg’s test demonstrated no obvious publication bias existed (Figure 6).

After two authors who used NOS including eight items with covers three aspects: selection, comparability, outcome assessed the quality of all studies, the result showed all the studies were the high quality (Figure 7).

Figure 5: Subgroup analysis of different blood transfusion percentage of TIVA compared INVA in overall survival (A) and in recurrence-free survival (B). Left is in favor of TIVA, but right is in favor of INVA.

Figure 6: (A) Begg’s funnel plots to detect the publication bias of eligible trials on OS by anesthesia (TIVA vs INVA). (B) Begg’s funnel plots to detect the publication bias of eligible trials on RFS by anesthesia (TIVA vs INVA).

5. Discussion
This meta-analysis showed that the TIVA for the maintenance of anesthesia during tumor operations is association with longer OS and RFS compared with INVA. In this meta-analysis, we did a subgroup analysis according to the type of tumor, the proportion of blood transfusion, respectively, and found that TIVA had a better survival rate in gastrointestinal tumors. With a higher proportion of blood transfusion, the advantages of TIVA were more certain than INVA.

By secreting the immunosuppressive effect of proinflammatory and anti-inflammatory cytokines, surgery can promote tumor cells to escape from the immune system, and anesthesia plays an indirect role in this process, so the time of anesthesia is also an important factor affecting the prognosis of tumors [21, 22]. Propofol induces cell apoptosis and inhibits tumor growth by activating the internal and external apoptosis pathways of hl-60 leukemia cells, and it also inhibited the growth of lymphoma cells in EL4 mice by activating CTLs [23-25]. Propofol significantly inhibited the migration and invasion of MDA-MB-231 cells. Propofol reduced the expression, secretion and phosphorylation of matrix metalloprotein (MMP)-2 and 9, and promoted the invasion and metastasis of cancer cells [26, 27]. Propofol induces the death of mda-mb-435 cells through the inactivation of mir-24/p27 signaling pathway, thereby inhibiting the growth of breast cancer tumor cells [27-29]. Exposure to inhaled anesthetics increases the potential for tumor migration. Propofol exerts an inhibitory effect on the formation of the breast layer of breast cancer stem cells (BCSCs) through pd-l1 mediation, so as to improve the prognosis and survival rate of breast cancer patients [30]. Isoflurane increases the mRNA expression of chemokine receptor type (CXCR)-2, metalloprotein-
ase (MMP)-11, and transforming growth factor (TGF)-β in ovarian cancer cells, promoting tumor growth and metastasis [31]. The clinically relevant concentration and incubation time of isoflurane can promote the survival and mobility of u251-gscs, suggesting that isoflurane can promote the growth and migration of glioblastoma to a certain extent [32]. Surgery can cause neuroendocrine, cytokines and metabolic components of the stress response [13]. Stress during general anesthesia and surgery directly activates the hypothalamic-pituitary-adrenal gland to suppress the immune response (HPA) axis and sympathetic nervous system, thereby affecting the prognosis of tumors [33, 34].

Inhaled anesthetics can up-regulate cell signal transduction and protein expression related to tumor metastasis and directly promote the metastasis of tumor cells [35]. In this meta-analysis, we made a subgroup to analyse the effect of transfusion on prognosis. Perioperative Blood Transfusion Anemia is an ominous sign for the cancer patient, and large evidence suggests that blood transfusion constitutes an independent risk factor for the prognosis of cancer patients [21]. Red blood cell transfusion may affect the sensitivity of HLA antigen, leading to various postoperative complications and affecting survival and prognosis [36]. Blood transfusions were found to be an independent and important risk factor for cancer progression, leading to a fourfold increase in lung tumor retention and a doubling of mortality [37]. The effects of anesthesia on tumor prognosis and blood transfusion on tumor prognosis may be mutually reinforcing.

**Figure 7:** The bias assessment of eligible trials.
Quality assessment of included studies. Quality assessment was conducted using the Cochrane risk of bias assessment tool. Risk of bias assessment for included studies in meta-analysis was classified as “high”, “low”, or “unclear”. (A, C) Quality assessment of cohort studies, (B, D) Quality assessment of randomized controlled trial.
Our result of this meta-analysis was great significance to certify that INVA can provide a better long-term survival and recurrence free survival after tumor surgery. Recently, many people have studied the effects of anesthesia, especially the effect of intravenous anesthesia and inhalation anesthesia on tumor prognosis of recurrence and survival. To explore the effect of selection of anesthetic drugs (propofol and diflurane) on long-term survival and tumor recurrence after colon cancer surgery in November 2018, and the retrospective studies showed the difference outcomes that the TIVA offered a better long-term survival relative to INVA and reduced the perioperative recurrence but some studies proved TIVA wasn’t association with OS and RFS [2, 16]. For current study, it included data from various retrospective and prospective studies, assessed the risk of bias, and a comprehensive analysis produced a more convincing result.

Nowadays, general anesthesia (intravenous and inhalation) and local anesthesia (nerve block) are commonly used in clinical practice. A large number of studies have proved that anesthesia affects the occurrence and recovery quality of postoperative complications through multiple immune pathways, as well as inflammatory and endocrine pathway [4, 38-40]. To some extent, it hinders the progress of the surgery and restricts the use of anesthesia. The choice of anesthetic method has become a difficult problem in clinical surgery. Although the mechanism of anesthetic method for carcinoma of urinary bladder and breast cancer is more specific than other types of cancer [41, 42], the evidence is not sufficient, and controversial issues remain. This meta-analysis provides more sufficient evidence to prove that intravenous anesthesia has a better survival rate than inhalation anesthesia, which is of great significance in guiding the clinical use of anesthesia. With the discovery of a large number of studies, it is believed that the use of anesthesia in clinical operations will be more standardized and optimized.

6. Limitations

We searched on PubMed for cohort studies about the effect of TIVA and INVA on cancer on survival to make a meta-analysis. This meta-analysis has multiple limitations, such as the benefit effect on oncological outcome that TIVA may reduce the perioperative recurrence remain unknown. The cohort studies included are retrospective and some studies used some factors to match the patients, but some factors may be unaccounted for, most importantly are that a number of factors (TNM stage, Postoperative NSAIDs, Postoperative metastasis, Surgery time, Anesthesia time and baseline characteristics) would affect the discrepancy of outcome. Although the improvement of OS and RFS was confirmed to be related to TIVA rather than INVA in the results of this meta-analysis, but among the 21 articles, five of them did not directly give HR value and CI, which needed to be extracted by Engauge Digitizer. In this process, even repeated extraction caused some errors to the final results. When using NOS to evaluate the quality of the studies, because most studies were retrospective studies, the results were analyzed by looking up the electronic disease history, and some studies did not describe the number of lost visitors or the treatment in the paper, resulting in a high risk of follow-up in the quality evaluation. In the subgroup analysis, the lack of literature data leads to incomplete analysis, insufficient evidence, and low persuasiveness. Blood transfusion is also an important independent risk factor for tumor prognosis, and subgroup analysis found that it is highly likely to affect the results of this meta-analysis. The different types of recurrence survivals (e.g., recurrence-free survival (RFS), disease free survival (DFS), progression-free survival (PFS)) are a challenge to compare the difference. Further, Because of insufficient data and different tumor types, we didn’t do a analysis with the single-group rate, and some studies evaluate the period of overall survival is too short to achieve a significant conclusion. Finally, patients in some studies not just use one type of anesthesia, and second type of anesthesia would influence the outcome.

7. Conclusion

In conclusion, this meta-analysis shows the TIVA may offer a better long-term survival and RFS after cancer surgery relative to INVA. TIVA is a potential to use in Maintenance of surgical anesthesia and many views had been proposed to explain this mechanism, but none has been proven. So further Prospective randomized controlled trials need to assess whether the TIVA can offer a long-term survival and reduce recurrence after tumor surgery related to INVA.

8. Author’s Contribution

Conception and design: Hengrui Liang, Wenhua Liang, Jianxing He; (II) Administrative support: Jianxing He; (III) Provision of study materials: Shuxian Qiu, Hengrui Liang; (IV) Collection and assembly of data: Shuxian Qiu; (V) Data analysis and interpretation: Shuxian Qiu, Hengrui Liang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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