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REVIEW ARTICLE/BRIEF REVIEW

Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous *versus* volatile anesthesia

Technique d'anesthésie et pronostics de cancer : une méta-analyse analyse comparant l'anesthésie intraveineuse totale et l'anesthésie par inhalation

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Abstract

Purpose *Cancer-related mortality, a leading cause of death worldwide, is often the result of metastatic disease recurrence. Anesthetic techniques have varying effects on innate and cellular immunity, activation of adrenergic-inflammatory pathways, and activation of cancer-promoting cellular signaling pathways; these effects may translate into an influence of anesthetic technique on long-term cancer outcomes. To further analyze the effects of propofol (intravenous) and volatile (inhalational gas) anesthesia on cancer recurrence and survival, we undertook a systematic review with meta-analysis.*

Source *Databases were searched up to 14 November 2018. Comparative studies examining the effect of inhalational volatile anesthesia and propofol-based total intravenous anesthesia (TIVA) on cancer outcomes were included. The Newcastle Ottawa Scale (NOS) was used to assess methodological quality and bias. Reported hazard ratios (HRs) were pooled and 95% confidence intervals (CIs) calculated.*

Principal findings *Ten studies were included; six studies examined the effect of anesthetic agent type on recurrence-free survival following breast, esophageal, and non-small cell lung cancer (n = 7,866). The use of TIVA was associated with improved recurrence-free survival in all cancer types (pooled HR, 0.78; 95% CI, 0.65 to 0.94; P < 0.01). Eight studies (n = 18,778) explored the effect of anesthetic agent type on overall survival, with TIVA use associated with improved overall survival (pooled HR, 0.76; 95% CI, 0.63 to 0.92; P < 0.01).*

This article is accompanied by an editorial. Please see Can J Anesth 2019; 66: this issue.

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Conclusion *This meta-analysis suggests that propofol-TIVA use may be associated with improved recurrence-free survival and overall survival in patients having cancer surgery. This is especially evident where major cancer surgery was undertaken. Nevertheless, given the inherent limitations of studies included in this meta-analysis these findings necessitate prospective randomized trials to guide clinical practice.*

Trial registration *PROSPERO (CRD42018081478); registered 8 October, 2018.*

Résumé

Objectif *La mortalité liée au cancer, une cause majeure de décès dans le monde entier, est bien souvent le résultat de la récurrence de la maladie métastatique. Les techniques anesthésiques ont des effets variés sur l'immunité naturelle et cellulaire, l'activation des voies adrénergiques inflammatoires, et l'activation des voies de signalisation cellulaire promouvant le cancer; ces effets pourraient se traduire dans une influence de la technique anesthésique sur les pronostics de cancer à long terme. Afin d'approfondir l'analyse des effets de l'anesthésie au propofol (voie intraveineuse) et par inhalation (gaz) sur la récurrence du cancer et la survie, nous avons entrepris une revue systématique avec méta-analyse.*

Source *Nous avons réalisé des recherches dans les bases de données jusqu'au 14 novembre 2018. Les études comparatives examinant l'effet d'une anesthésie par inhalation et d'une anesthésie intraveineuse totale (TIVA) avec propofol sur les pronostics de cancer ont été incluses dans notre revue. L'échelle de Newcastle-Ottawa (NOS) a été utilisée pour évaluer la qualité méthodologique et le biais. Les rapports de risque (RR) rapportés ont été pondérés et les intervalles de confiance (IC) à 95 % calculés.*

Constatations principales *Dix études ont été incluses; six études ont examiné l'effet du type d'agent anesthésique sur la survie sans récurrence après un cancer du sein, de l'œsophage et du cancer pulmonaire non à petites cellules (n = 7866). L'utilisation d'une TIVA était associée à une amélioration de la survie sans récurrence, tous types de cancer confondus (RR pondéré, 0,78; IC 95 %, 0,65 à 0,94; P < 0,01). Huit études (n = 18 778) ont exploré l'effet du type d'agent anesthésique sur la survie globale, l'utilisation d'une TIVA étant alors associée à une amélioration de la survie globale (RR pondéré, 0,76; IC 95 %, 0,63 à 0,92; P < 0,01).*

Conclusion *Cette méta-analyse suggère que l'administration d'une TIVA à base de propofol pourrait être associée à une amélioration de la survie sans récurrence et de la survie globale chez les patients subissant une chirurgie oncologique. Cette observation est particulièrement frappante dans les cas de chirurgie oncologique majeure. Toutefois, étant donné les lacunes inhérentes des études incluses dans cette méta-analyse, ces résultats nécessitent la réalisation d'études randomisées prospectives afin d'éclairer la pratique clinique.*

Enregistrement de l'étude *PROSPERO (CRD42018081478); enregistrée le 8 octobre 2018.*

Cancer is one of the leading causes of death worldwide, with most patients dying from metastatic disease.[1] It is currently estimated that more than 60% of patients with cancer will require surgery for the removal of solid tumours.[2] The processes of tissue trauma, surgical manipulation of the tumour, and exposure to the physiologic stresses of the perioperative period can result in impaired local and cellular immunity, with consequent loco-regional recurrence and metastasis.[3-5] The degree to which general anesthetic technique (inhalational volatile agents, or total intravenous anesthesia [TIVA] with propofol) contributes to this patient vulnerability in the perioperative period is an area of particular interest.[5]

Preclinical studies have found that both intravenous and volatile anesthetic agents alter the biology of cancer and immune cell lines by directly activating cellular receptors and cell signaling pathways, as well as by altering cellular kinetics and gene transcription.[3,6,7] Anesthetic technique may also affect cell-mediated immunity and promote spread in different cancer types.[8]

A recent systematic review published by Soltanizadeh *et al*. examined outcomes of cancer surgery after inhalational *vs* intravenous anesthesia, but was constrained by the inclusion of studies that focused on postoperative complications or studies that did not have cancer recurrence or survival as the primary endpoint.[9] We conducted this meta-analysis to provide an up-to-date assessment of the current evidence for the impact of type of anesthesia for cancer surgery on long-term clinical outcomes (cancer recurrence and overall survival).

Methods

Our results are reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines) and this review was registered on 8 October, 2018 with PROSPERO (registration number: CRD42018081478).

Study eligibility criteria

All randomized-controlled trials (RCTs) and observational longitudinal studies (prospective or retrospective) evaluating the effects of TIVA and inhalational anesthetic agents on cancer outcomes in patients undergoing cancer surgery were included. We excluded animal studies, studies not published in English, studies with insufficient information to perform the meta-analysis (such as no cancer-related endpoint), studies that did not report separate data for each intervention group with a measure of effect (such as hazard ratio [HR] or Peto odds ratio), or studies that focused on other interventions (e.g., perioperative chemotherapy and/or radiation therapy).

Information sources

The databases initially searched were Medline (through Ovid), EMBASE (through Ovid), The Cochrane Library, Web of Science, and PubMed from the start of inception until 17 March 2017, with a search update performed in PubMed and in sources of grey literature until 14 November 2018. Sources of grey literature included Open Grey and Google Scholar®. Conference proceedings and abstracts were searched in Web of Science. EndNote software (Clarivate Analytics, Philadelphia, PA, USA) was used to store all citations for duplicate checking.

Search

An experienced librarian (G.P.) developed a comprehensive search strategy that included broad terms such as "cancer", "tumor", "neoplasms", "perioperative", "anesthesia", and narrow terms such as "TIVA", "propofol", "volatile", and "sevoflurane" among other anesthetic intervention terms. The complete Medline search strategy and the terms for the search update are reported in Appendix 1.

Study selection

Eligibility assessments were performed independently by three teams of reviewers on behalf of the Global Onco-Anesthesia Research Collaboration Group (Acknowledgment). Cohen's kappa coefficient, which describes the level of inter-rater agreement, was calculated. Disagreements at all stages were resolved through discussion. If agreement could not be reached, a third reviewer (B.R.) made a final decision.

Data collection process and data items

One reviewer (A.Y.) extracted data from individual studies and another reviewer (M.L.O.) cross-checked the information. The following information was extracted from each study: i) general information such as title, authors, publication year, and country; ii) study characteristics such as study design, setting, sample size, and outcome assessed; iii) participant characteristics such as number of patients within each group, age (mean and range) and type of cancer; and iv) intervention characteristics such as details of anesthetic techniques (volatile agents used, TIVA agent used), concomitant drug (opiates, anti-inflammatories and blood transfusions), or regional anesthesia use.

Risk of bias in individual studies

One reviewer (A.Y.) assessed the risk of bias of the included studies and another reviewer (B.R.) cross-checked the information. For RCTs, we used the Cochrane risk of bias tool. The potential of bias was appraised in five domains: selection, performance, detection, attrition, and reporting. These domains specifically evaluate how the random sequence was generated, methods of allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, how incomplete outcome data were handled, and if there was evidence of selective outcome reporting. Each potential source of bias was graded as low, unclear, or high, and a justification for each judgment was provided. Observational studies were evaluated using the Newcastle Ottawa Scale (NOS),[10] which assesses the potential for bias by scoring the selection process of the study groups, comparability of the groups, and ascertainment of exposure and outcome in the studies. Studies can be awarded a maximum of one point for each domain with an additional point being awarded for studies controlling for additional confounders. The maximum score allocated in the selection domain is 4 points, in the comparability domain is 2 points and outcome domain is 3 points. A maximum score of 9 points can be achieved and a higher score (≥ 7 points) indicates a lower risk of bias.[11]

Summary measures

The primary outcome measures for this meta-analysis were recurrence-free survival and overall survival. Adjusted HR from Cox proportional hazard models, their respective 95% confidence intervals (CI), and the *P* values were extracted from each of the studies. Where more than one data set was given, multivariate analysis data were used. If this was not

provided, propensity matched data, if available, were used instead.

Synthesis of results

Analyses were conducted using Review Manager (RevMan version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We converted the reported HRs into log HRs and used the generic inverse-variance method with random-effects model to pool the data. To maintain TIVA as a reference group across studies, we inverted the HR (1/HR) for studies reporting volatiles as a reference group. When data were provided in Kaplan Meier plots, an attempt was made to contact the study authors for further data. When the estimates differed substantially among the pooled studies (Chi squared test, $P = 0.10$), we conducted a sensitivity analysis by eliminating the outliers.

Additional analyses and risk of bias across studies

We *a priori* planned to explore sources of heterogeneity with subgroup analyses or meta-regression as well as using a funnel plot and a regression asymmetry test to assess small-study bias. Because of the small number of studies included, this was not done.

Results

Study selection

Figure 1 shows the study selection flowchart. We retrieved 12,508 citations and after removal of duplicates, there were 9,536 unique citations. After review, one prospective RCT and nine retrospective studies that pertained to volatile anesthesia and propofol-TIVA were included in the final analysis.[12-21]

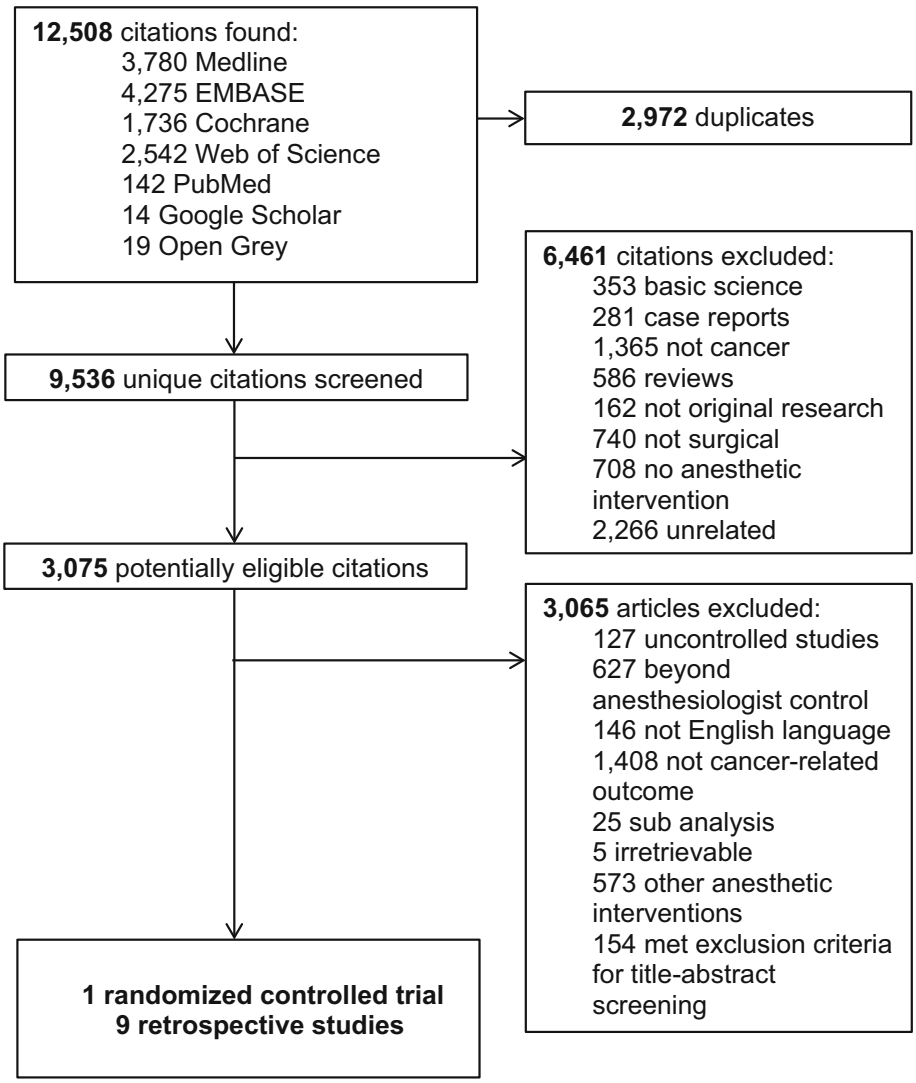


Fig. 1 PRISMA flow diagram of study selection

Study characteristics and risk of bias within studies

Table 1 shows the study characteristics and Table 2 the recorded event rates (cancer recurrence or death). All the nine retrospective studies had a NOS $\geq$ 7 demonstrating good methodologic quality and a low risk of bias.[12-18,20,21] The single prospective RCT included in this meta-analysis had a low risk of bias for each domain.[19]

Results of individual studies

Patients receiving a propofol infusion only, or a propofol and remifentanil infusion during their surgery were categorized into the TIVA group; patients receiving sevoflurane, isoflurane, desflurane or enflurane were categorized into the volatile group. All studies except Yan *et al.*[19] adjusted for at least one of the following variables in their multivariate analyses: age, body mass index, comorbidities, preoperative therapy, pathologic stage or grade of cancer, and intraoperative anesthetic interventions such as epidural or blood transfusion.[12-18,20,21]

Synthesis of results

Recurrence-free survival

Six studies (five retrospective[13-16,20] and one RCT)[19] examined the effects of TIVA and volatile agents on recurrence-free survival in breast, esophageal, and non-small cell lung cancer (Fig. 2). The total sample size was 7,866 patients. When compared with volatile anesthesia, the use of TIVA was associated with improved recurrence-free survival in these cancer types (pooled HR, 0.78; 95% CI, 0.65 to 0.94; $P < 0.01$).

Overall survival

Eight studies (seven retrospective[12,13,16-18,20,21] and one RCT),[19] that included a total of 18,778 patients, provided ten HRs for this analysis (Fig. 3) in breast, colorectal, gastric, esophageal, and non-small cell lung cancer, and mixed cancer types. There was an associated improvement in overall survival with TIVA use when compared with volatile anesthesia (pooled HR, 0.76; 95% CI, 0.63 to 0.92; $P < 0.01$).

There was substantial heterogeneity among the studies and to explore it, outliers were removed (four estimates: Jun *et al.*,[13] Wigmore *et al.*,[17] Wu *et al.*[18] and Zheng *et al.*).[21] This gave an inconsistency score of 0% and a resulting pooled HR of 0.97 (95% CI, 0.85 to 1.11; $P = 0.66$). Unsuccessful strategies to further decrease the inconsistency score included removing the only RCT, removing the one study with multiple estimates (Enlund *et al.*),[12] and leaving studies with positive estimates only.

Discussion

Despite advances in modern medicine, cancer is still a leading cause of death worldwide.[22] It is therefore vital that clinicians consider all aspects of cancer care, including the delivery of anesthesia during cancer resection surgery, to optimize patients' cancer outcomes. The pooled results from this meta-analysis suggest that TIVA use (compared with volatile anesthesia) during cancer surgery is associated with improved recurrence-free survival and overall survival across numerous cancer types. Breast cancer was the most often examined tumour type with five studies reporting on outcomes after breast cancer surgery[12,14,15,19,20]; in this population, TIVA use was associated with an improvement in recurrence-free survival but not overall survival.

The inconsistency in results between the individual studies included within the meta-analysis for breast cancer outcomes may be explained by confounding factors such as the degree of surgical trauma.[23] In the study by Kim *et al.*, where no benefit was reported with TIVA use across all types of breast cancer surgery, it is important to note that of those patients who had suffered recurrence, 73% of patients had undergone mastectomy.[14] Similarly, in the study by Yoo *et al.*, patients undergoing total mastectomy were associated with higher risks of cancer recurrence and all-cause mortality when compared with breast-conserving surgery.[20] In the study by Lee *et al.,* all of the patients underwent modified radical mastectomies and had a lower rate of cancer recurrence with TIVA use when compared with the sevoflurane group.[15] Enlund *et al.* examined overall survival in patients with breast cancer but did not specify the type of surgical procedure.[12] Importantly, the five-year survival rate for breast cancer is 88.9%, and thus the 50-70 month follow-up time in this study by Enlund *et al.*[12] may not be sufficient to detect a meaningful difference of the effect of anesthesia type on survival.[24]

Preclinical studies suggest that drugs used for general anesthesia affect cellular immunity and potentiate cancer spread.[3,25] Mechanistic studies have examined the differential effects of anesthetic agents on tumour cell biology, with *in vitro* data strongly supporting a pro-metastatic effect of volatile anesthesia and an anti-metastatic effect of propofol.[3] *In vitro* studies investigating the effect of different volatile agents have found an increased expression of cellular mediators that promote cancer cell proliferation, resistance of apoptosis by tumour cells, a propensity to invasion and migration of cells, endothelial-mesenchymal transition, basement

Table 1 Characteristics of each study

Study	Sample size	Study design	Risk of bias assessment	Cancer type	Intravenous agents used	Volatile agents used (± remifentanil infusion)	Cancer outcomes assessed
Enlund *et al.*[12]	Total: 2,838	Retrospective cohort	NOS score 7	Breast	Propofol	Sevoflurane	Overall survival
2014	TIVA: 903			Colon	Epidural anesthesia performed in colorectal cancer patients only	Epidural anesthesia performed in colorectal cancer patients only	
Sweden	Volatile: 1,935			Rectal			
Jun *et al.*[13]	Total: 922	Retrospective cohort	NOS score 7	Esophageal	Propofol	Isoflurane	Recurrence-free survival
2017	TIVA: 731				Remifentanil	Sevoflurane	
South Korea	Volatile: 191				90.2% received epidural anesthesia	Desflurane	Overall survival
						Remifentanil	
						76.4% received epidural anesthesia	
Kim *et al.*[14]	Total: 2,645	Retrospective cohort	NOS score 8	Breast	Propofol	Sevoflurane	Recurrence-free survival
2017	TIVA: 56				Remifentanil	Desflurane	
South Korea	Volatile: 2,589				Regional anesthesia information not provided	Isoflurane	Overall mortality*
						Enflurane	
						Remifentanil	
						Regional anesthesia information not provided	
Lee *et al.*[15]	Total: 325	Retrospective cohort	NOS score 8	Breast	Propofol	Sevoflurane	Recurrence-free survival
2016	TIVA: 173				Regional anesthesia information not provided	Regional anesthesia information not provided	Overall survival†
South Korea	Volatile: 152						
Oh *et al.*[16]	Total: 362 ‖	Retrospective cohort	NOS score 8	NSCLC	Propofol	Sevoflurane	Recurrence-free survival
2018	TIVA: 181				Remifentanil	Remifentanil	
South Korea	Volatile: 181				No regional technique	No regional technique	Overall survival
Wigmore *et al.*[17]	Total: 7,030	Retrospective cohort	NOS score 7	Breast	Propofol	Isoflurane	Overall survival
	TIVA: 3,714			Gastrointestinal	Remifentanil	Sevoflurane	
2016	Volatile: 3,316			Gynecology	9% received epidural anesthesia	12% received epidural anesthesia	
United Kingdom				Sarcoma			
				Urology			
				Other ‡			
Wu *et al.*[18]	Total: 1,363	Retrospective cohort	NOS score 7	Colon	Propofol	Desflurane	Overall survival
2018	TIVA: 657				No regional technique	No regional technique	Disease-free survival*
China	Volatile: 706						
Yan *et al.*[19]	Total: 80	Prospective randomized-controlled trial	Cochrane risk of bias assessment Low risk of bias for all areas	Breast	Propofol	Sevoflurane	Recurrence-free survival§
2018	TIVA: 40				Remifentanil	No regional technique	
China	Volatile: 40				No regional technique		Overall survival§

Table 1 continued

Study	Sample size	Study design	Risk of bias assessment	Cancer type	Intravenous agents used	Volatile agents used (± remifentanil infusion)	Cancer outcomes assessed
Yoo *et al.*[20]	Total: 3,552 ‖	Retrospective cohort	NOS score 8	Breast	Propofol	Enflurane	Recurrence-free survival
2019	TIVA: 1,776				Remifentanil	Isoflurane	
South Korea	Volatile: 1,776				No regional technique	Sevoflurane	Overall survival
						Desflurane	
						No regional technique	
Zheng *et al.*[21]	Total: 2,856	Retrospective cohort	NOS score 7	Gastric	Propofol	Sevoflurane	Overall survival
2018	TIVA: 1,506				Remifentanil	Remifentanil	
China	Volatile: 1,350				Regional anesthesia information not provided	Regional anesthesia information not provided	

*Outcome not assessed in meta-analysis; †Unable to obtain raw data for overall survival from authors; ‡Skin (mainly melanoma), head and neck or lymphoma patients having splenectomies; §Secondary analysis; ‖Propensity matched data used. NOS = Newcastle Ottawa Scale; NSCLC = non-small cell lung cancer; TIVA = total intravenous anesthesia.

membrane degradation, and angiogenesis.[26-31] In contrast, when tumour cells are exposed to propofol, apoptosis is preserved and cell proliferation is reduced.[32-35]

Volatile anesthesia's alteration of immune function has also been implicated in its hypothesized pro-metastatic potential through manipulation of the perioperative immune response.[3] Preclinical data have reported impaired immune cell number and function after exposure to volatile anesthesia in animal models of cancer.[3,25,36,37] Volatile agents reduce natural killer cell activity, a cytotoxic lymphocyte in the innate immune system and critical in the anti-tumour immune response.[36,38,39] Reduced natural killer cell activity has been linked to tumour cell dissemination in patients with cancer.[40-42] In contrast, *in vitro* studies report that propofol does not affect natural killer cell activity.[39] Propofol may also reduce hypoxia-inducible factor 1α (HIF-1α) levels, a key regulator in the response to tumour growth.[30] Activation of HIF-1α occurs during low oxygen states and promotes cell proliferation, angiogenesis, and metastasis[43]; this has been reported to be activated by volatile agents.[26,30,44]

It is therefore plausible that anesthesia technique is a critical component in cancer progression. Volatile agents may potentially "fuel the fire" and contribute to inherent cancer and surgical wounding processes characterized by pro-adrenergic, pro-inflammatory, immunomodulatory, and pro-angiogenic signalling.[5] No single pathway, however, has been implicated, suggesting heterogeneity of the underlying drivers of cancer recurrence. Other clinically relevant interventions in the perioperative period, including surgical extent, blood transfusion, hypothermia, and administration of other medications (e.g., opioids, beta-blockers, anti-inflammatories, steroids), may themselves impact cancer cell biology.[5]

Surgical trauma activates neuroendocrine, inflammatory, immunologic, and metabolic pathways.[45] These changes reduce innate and cellular immunity and may promote cancer spread postoperatively.[46] Postoperative complications, including wound complications, pulmonary infections, and anastomotic leaks, have been reported to increase cancer recurrence and reduce overall survival.[47,48] Such complications are characterized by exaggerated inflammatory processes. It is important to note that postoperative complications after cancer surgery have also been reported to be associated with anesthetic technique. De la Gala *et al.* noted a reduction in postoperative pulmonary complications and one year mortality with sevoflurane use (compared with, TIVA) in patients undergoing lung resection surgery.[49] Conversely, Chang *et al.* noted fewer pulmonary complications and reduced mortality with TIVA use in patients with head and neck cancer undergoing free flap surgery when compared with volatile anesthesia.[50]

Table 2 Number of patients with events (cancer recurrences or death) reported

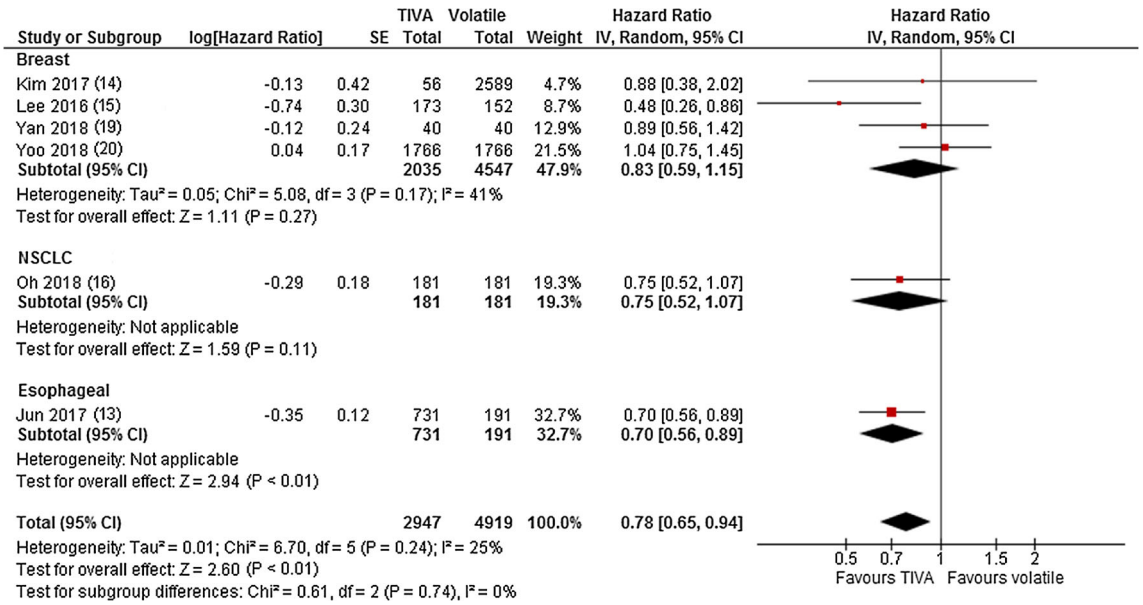
Study name and cancer types examined	Median follow-up (months)	Event/no (%)	
		TIVA	Volatile
Recurrence:			
Jun *et al.*[13]	38	315/731 (43.1) Ω	109/191 (57.1) Ω
- Esophageal			
Kim *et al.*[14]	70	6/56 (10.7)	227/2589 (8.8)
- Breast			
Lee *et al.*[15]	60	20/173 (11.6)	29/152 (19.1)
- Breast			
Oh *et al.*[16]	60	n/a	n/a
- NSCLC			
Yan *et al.*[19]	28	2/40 (5.0)	6/40 (15.0)
- Breast			
Yoo *et al.*[20]	67 (TIVA)	118/1,766 (6.7)	108/1,766 (6.1)
- Breast	53 (volatile)		
Deaths:			
Enlund *et al.*[12†]	60		
- Colon		66/179 (37.0)	243/516 (47.1)
- Rectal		28/104 (27.0)	67/202 (33.0)
- Breast		99/620 (16.0)	219/1217 (18.0)
Jun *et al.*[13]	38	284/731 (36)	98/191 (51)
- Esophageal			
Lee *et al.*[15]	60	9/173 (5.2)	11/152 (7.2)
- Breast			
Oh *et al.*[16]	60	n/a	n/a
- NSCLC			
Wigmore *et al.*[17]	32	103/1560 (6.6)	52/603 (8.6)
- Breast		137/418 (32.8)	223/504 (44.2)
- Gastrointestinal		81/331 (24.5)	133/428 (31.1)
- Gynecology		77/491 (15.7)	128/625 (20.5)
- Sarcoma		41/670 (6.1)	81/432 (18.8)‖
- Urology		65/244 (26.6)	179/724 (24.7)
- Other ‡			
Wu *et al.*[18]	44.4 (TIVA)	88/657	307/706
- Colon	38.4 (volatile)		
Yan *et al.*[19]	28	1/40 (2.5)	1/40 (2.5)
- Breast			
Yoo *et al.*[20]	67 (TIVA)	116/1766 (6.6)	103/1766 (5.8)
- Breast	53 (volatile)		
Zheng *et al.*[21§]	43.6 (TIVA)	n/a	n/a
- Gastric	39.7 (volatile)		

NSCLC = non-small cell lung cancer; TIVA = total intravenous anesthesia

ΩNumbers taken from five-year data; †Data calculated from Table 3 (1 minus the proportion of patients surviving at five years); ‡Skin (mainly melanoma), head and neck or lymphoma patients having splenectomies; §Authors contacted but no response; ‖Data obtained from study authors; n/a = not available

Postoperative complications may adversely affect postoperative recovery and reduce the ability to "Return to Intended Oncologic (adjuvant) Therapy" (RIOT) in the immediate postoperative period.[51]

Surveys of current clinical practice report that anesthesiologists generally have a preference for volatile anesthesia.[52,53] In a survey of Australasian anesthesiologists, Lim *et al.* reported that > 80% of



Notes:

NSCLC= non-small cell lung cancer

Lee *et al.* (15) defined recurrence-free survival as the date of surgery to the date of first recurrence, which was clarified as loco-regional recurrence or distant metastases confirmed by clinical evidence or radiological examination.

Jun *et al.* (13) defined recurrence-free survival as the date of surgery to either the date of first recurrence or the date of death.

Kim *et al.* (14) defined recurrence-free survival as the date of the first curative surgery to the date of the first loco-regional or distant recurrence.

Oh *et al.* (16) defined recurrence-free survival as the period from surgery date to the date of recurrence or death.

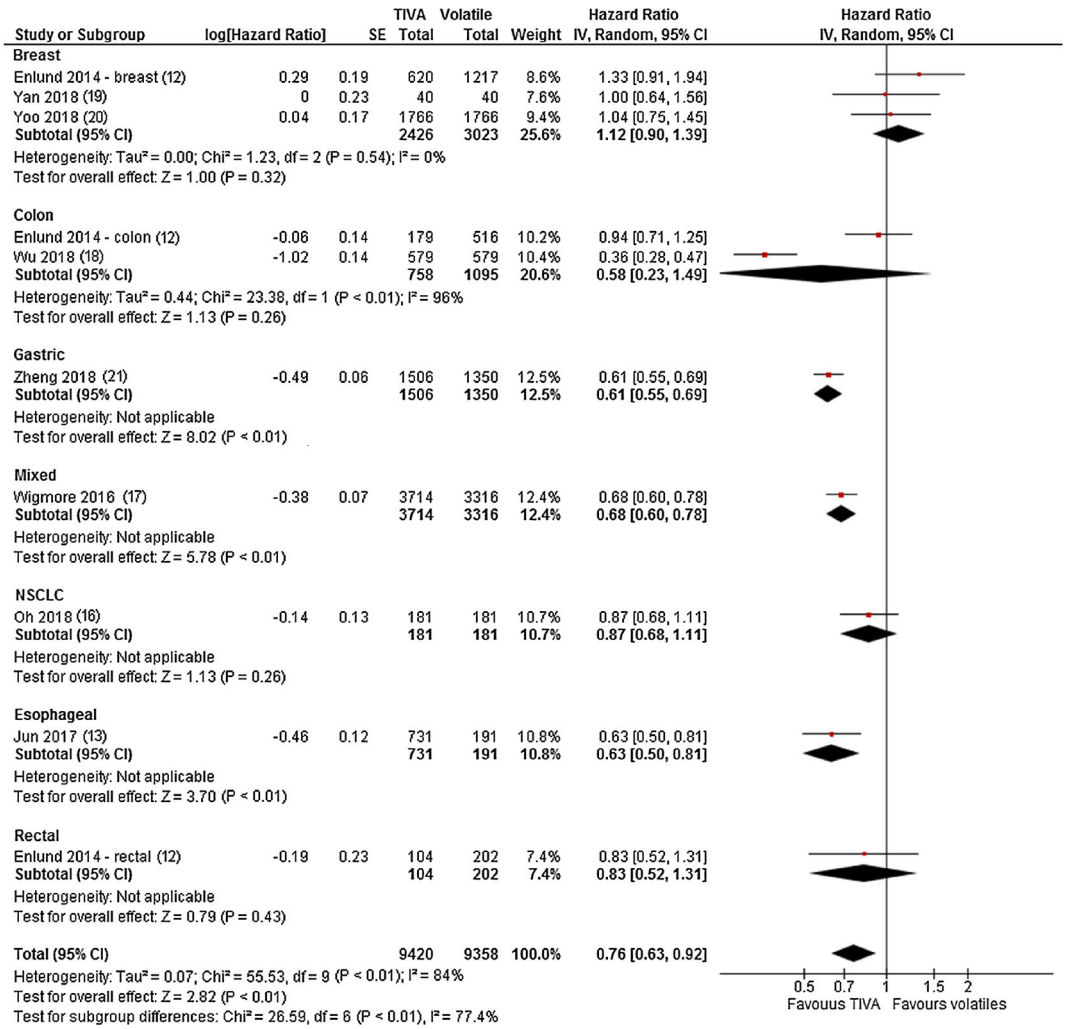
Yan *et al. (19)* defined recurrence-free survival as the time from the date of surgery till disease relapse confirmed by clinical evidence and radio- logical examination.

Yoo *et al. (20)* defined recurrence-free survival as the interval between the date of surgery and the date of recurrence of breast cancer or death.

Fig. 2 Recurrence-free survival

anesthesiologists prefer volatile-based anesthesia within their daily routine. Despite 43% of respondents reporting that they felt that TIVA may reduce cancer recurrence (compared with, inhalational anesthesia), only 29% reported regular use of TIVA for cancer surgery.[52] This propensity toward volatile-based anesthesia necessitates large prospective RCTs of TIVA *vs* volatile anesthesia to inform international clinical guidelines.

Limitations of this study include the retrospective nature of the majority of the studies. The studies also had different follow-up intervals and significant variability of baseline patient demographics. There were also differences in study characteristics, including variable sample sizes in the treatment arms,[13,14] unbalanced study populations (e.g., patients in one treatment group being older, having significant comorbidities),[18] different stages/grades of



Notes:
NSCLC= non-small cell lung cancer

Enlund *et al.* (12) Overall survival time was defined as the interval between date of surgery and date of outcome, emigration, or end of follow-up on 31 September 2012.

Jun *et al*. (13) Overall survival was calculated from the date of surgery to the date of death from any cause.

Oh *et al*. (16) Overall survival was defined as the period from surgery date to the date of death.

Wigmore *et al*. (17) Overall survival was defined from the date of surgery to the date of death.

Wu *et al*. (18) Survival time was defined as the interval between the date of surgery and the date of death, or March 31, 2017, for those who were censored.

Yan *et al. (19)* Overall survival was defined as the time from the date of surgery till death or last follow-up.

Yoo et al (20) Overall survival was defined as the interval from the date of surgery to the date of death.

Zheng *et al*. (21) Survival time was measured from the date of gastrectomy to death or to the last follow-up time before March 31, 2015.

Fig. 3 Overall survival

cancer, differences in anesthetic technique (e.g., remifentanil, different volatiles used, and difference in use of regional anesthesia), and differences in surgical technique (e.g., differences in surgical magnitude). This study was also limited by the availability of data within the published manuscripts for analysis. The possibility of publication bias (which could not be assessed because the overall number of included studies was too low) should also be considered as this has the potential to greatly affect the results of this meta-analysis. Given these limitations, while the results favour a positive impact of propofol-based TIVA on cancer outcomes, the data should be interpreted with caution.

Collectively, this meta-analysis examined over 21,000 cancer patients with multiple cancer types. Despite the heterogeneity of the study designs and data, including different cancer types, there is an association between improved cancer outcomes with propofol-based TIVA when compared with inhalational volatile-based anesthesia. The results of this meta-analysis, together with the growing body of preclinical literature in the field, support the hypothesis that choice of anesthetic drug may influence patient outcome after cancer surgery. To test the hypothesis, a number of prospective RCTs in specific cancer types are currently underway (Randomized, Open-label Study to Compare Propofol Anesthesia With Sevoflurane Anesthesia in Terms of Overall Survival in Patients With Surgical Intervention for either Breast-, Colon-, or Rectal Cancer [NCT01975064]; General Anesthetics in CAncer REsection Surgery [GA-CARES] Trial: Pragmatic Randomized Trial of Propofol *vs* Volatile Inhalational Anesthesia [NCT03034096]; Impact of Inhalational Versus Intravenous Anesthesia Maintenance Methods on Long-term Survival Rate in Elderly Patients After Cancer Surgery: an Open-label, Randomized-Controlled Trial [NCT02660411]; and Volatile Anaesthesia and Perioperative Outcomes Related to Cancer [VAPOR-C]: A Feasibility Study [ACTRN1261700106538]) and will help guide the optimal anesthesia choice for perioperative cancer care.

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Author contributions *Andrea Yap* contributed to all aspects of this manuscript, including conception and design; acquisition, analysis, and interpretation of data and drafting the article. *Maria A. Lopez-Olivo* contributed to acquisition, analysis, interpretation of data and drafting the article. *Julia Dubowitz* and *Jonathan Hiller* contributed to analysis, interpretation of data and drafting the article. *Bernhard Riedel* contributed to conception and design, analysis, and interpretation of data and drafting the article.

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Appendix 1 Search strategies

Medline (Ovid) – Inception until March 17, 2017

1 exp NEOPLASMS/su

2 ((cancer* or neoplas* or malignan* or tumor* or tumour* or metasta* or carcinoma* or oncolog* or recurrence* or chemotherapy* or chemo-therap* or antineoplas* or anti-neoplas*) and (patient* or surg* or resect*)).ti.

3 ((cancer* or neoplas* or malignan* or tumor* or tumour* or metasta* or carcinoma* or oncolog* or recurrence* or chemotherapy* or chemo-therap* or antineoplas* or anti-neoplas*) adj5 (patient* or surg* or resect*)).ti,ab.

4 or/1-3

5 exp PERIOPERATIVE PERIOD/

6 exp PERIOPERATIVE CARE/

7 (perioperativ* or peri-operativ* or intraoperativ* or intra-operativ*).ti.

8 ((pre-surg* or presurg* or post-surg* or postsurg* or preoperativ* or pre-operativ* or postoperativ* or post-operativ*) and (anesthe* or anaesthe* or analges* or block* or post-anesthe* or postanesthe* or post-anaesthe* or postanaesthe* or pre-anesthe* or preanesthe* or pre-anaesthe* or preanaesthe* or "fast track")).ti.

9 (((perioperativ* or peri-operativ* or intraoperativ* or intra-operativ* or pre-surg* or presurg* or post-surg* or postsurg* or preoperativ* or pre-operativ* or postoperativ* or post-operativ* or "fast track") adj5 (anesthe* or anaesthe* or analges* or block* or post-anesthe* or postanesthe* or post-anaesthe* or postanaesthe* or pre-anesthe* or preanesthe* or pre-anaesthe* or preanaesthe*)) and (cancer* or neoplas* or malignan* or tumor* or tumour* or metasta* or carcinoma* or oncolog* or recurrence* or chemotherapy* or chemo-therap* or antineoplas* or anti-neoplas*)).ab.

10 or/5-9

11 4 and 10 [Ca surg/pts + periop]

12 exp *PERIOPERATIVE PERIOD/ or exp *PERIOPERATIVE CARE/ or (perioperativ* or peri-operativ* or intraoperativ* or intra-operativ* or pre-surg* or presurg* or post-surg* or postsurg* or preoperativ* or pre-operativ* or postoperativ* or post-operativ* or post-anesthe* or postanesthe* or post-anaesthe* or postanaesthe* or pre-anesthe* or preanesthe* or pre-anaesthe* or preanaesthe*).ti. [periop focus]

13 exp *NEOPLASMS/su or (cancer* or neoplas* or malignan* or tumor* or tumour* or metasta* or carcinoma* or oncolog* or recurrence* or chemotherapy* or chemo-therap* or antineoplas* or anti-neoplas*).ti. [Ca focus]

14 exp *"ANESTHESIA AND ANALGESIA"/ or (anesthe* or anaesthe* or analges* or TIVA or ((nerve* or regional* or spinal* or neuraxial* or paravertebral*) adj3 block*)).ti. or (total* adj intravenous* adj3 (anesthe* or anaesthe* or technique*)).ti. [Anes focus]

15 ((perioperativ* or peri-operativ* or intraoperativ* or intra-operativ* or pre-surg* or presurg* or post-surg* or postsurg* or preoperativ* or pre-operativ* or postoperativ* or post-operativ* or post-anesthe* or postanesthe* or post-anaesthe* or postanaesthe* or pre-anesthe* or preanesthe* or pre-anaesthe* or preanaesthe*) adj5 (cancer* or neoplas* or malignan* or tumor* or tumour* or metasta* or carcinoma* or oncolog* or recurrence* or chemotherapy* or chemo-therap* or antineoplas* or anti-neoplas* or ((nerve* or regional* or spinal* or neuraxial* or paravertebral*) adj3 block*) or (total* adj intravenous* adj3 (anesthe* or anaesthe* or technique*)))).ab.

16 (12 and 13) or (13 and 14) or (12 and 14) [#1 focus]

17 (12 and 13) or (13 and 14) or (12 and 14) or (15 and (12 or 13 or 14)) [#2 focus]

18 exp "ANESTHESIA AND ANALGESIA"/

19 (anesthe* or anaesthe* or analges* or TIVA or (total* adj intravenous* adj3 (anesthe* or anaesthe* or technique*))).ti.

20 ((nerve* or regional* or spinal* or neuraxial* or paravertebral*) adj3 block*).ti.

21 ((anesthe* or anaesthe* or analges* or block*) adj3 (technique* or regional* or epidural* or peridural* or spinal* or neuraxial* or paravertebral*)).ab.

22 ((nerve* or regional* or spinal* or neuraxial* or paravertebral*) adj3 block*).ab.

23 ((analges* adj3 patient* adj3 control*) or TIVA or (total* adj intravenous* adj3 (anesthe* or anaesthe* or technique*))).ab.

24 or/18-23 [anes or analg or block terms]

25 11 and 24 [Ca surg/pts + periop + (anes or analg or block)]

26 exp ANESTHETICS/ or exp ANALGESICS, OPIOID/ or MORPHINE/ or HALOTHANE/ or ISOFLURANE/ or KETAMINE/ or THIOPENTAL/ or PROPOFOL/

27 ((volatile* or inhal* or induc*) and (anesthe* or anaesthe* or analges*)).ti.

28 ((volatile* or inhal* or induc*) adj3 (anesthe* or anaesthe* or analges*)).ab.

29 (lignocaine* or lidocaine* or bupivacaine* or ropivicaine* or clonidine* or morphine* or pethidine* or naloxone* or nalbuphine* or naltrexone* or fentanyl* or alfentanil* or sufentanil* or remifentanil* or codeine* or hydrocodone* or oxycodone* or demerol* or tramadol*).ti,rn.

30 (halothane* or enflurane* or flurane* or isofulrane* or sevoflurane* or desflurane* or ketamine* or thiopentone* or thiopental* or etomidate* or propofol* or (nitrous adj oxide*)).ti,rn.

Appendix continued

31 or/26-30 [anesthetic MeSH or KW terms]

32 11 and 31 [Ca surg/pts + periop + anesthetics]

33 exp ADRENERGIC BETA-ANTAGONISTS/ or PROPRANOLOL/ or ISOPROTERENOL/ or ATENOLOL/ or BISOPROLOL/ or METOPROLOL/ or exp ADRENERGIC ALPHA-AGONISTS/ or CLONIDINE/ or DEXMEDETOMIDINE/

34 ((beta adj5 (blocker* or blocking)) or (adrenergic* adj5 beta adj5 (block* or antagonist*)) or (adrenergic* adj5 alpha adj5 agonist*)).ti.

35 (propanolol* or Isoproterenol* or atenolol* or bisoprolol* or metoprolol* or clonidine* or dexmedetomidine*).ti,rn.

36 ((beta adj3 (blocker* or blocking)) or (adrenergic* adj3 beta adj3 (block* or antagonist*)) or (adrenergic* adj3 alpha adj3 agonist*)).ab.

37 or/33-36 [beta-blocker terms]

38 11 and 37 [Ca + periop + beta-blockers]

39 exp *ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL/ or Anti-Inflammatory Agents, Non-Steroidal.rn. or *KETOROLAC/ or *DICLOFENAC/ or *ACETAMINOPHEN/ or *IBUPROFEN/ or *ASPIRIN/ or exp *SERINE PROTEINASE INHIBITORS/ or *APROTININ/ [NSAID etc MeSH MJ]

40 (((nonsteroidal or non-steroidal) adj3 anti-inflammatory adj3 (drug* or agent*)) or ((COX or COX2 or cyclooxygenase* or cyclo-oxygenase*) adj5 inhibit*) or (serine* adj5 (protease* or proteinase*) adj5 inhibit*)).ti.

41 (NSAID* or aspirin* or ketorolac* or diclofenac* or etedolac* or acetaminophen* or tylenol* or paracetamol* or ibuprofen* or celecoxib* or parecoxib* or rofecoxib* or valdecoxib* or etoricoxib* or gabapentin* or pregabalin* or aprotinin*).ti,rn.

42 (((COX or COX2 or cyclooxygenase* or cyclo-oxygenase*) adj3 inhibit*) or (serine* adj3 (protease* or proteinase*) adj3 inhibit*)).ab.

43 (LIDOCAINE/ or MAGNESIUM/) and (ANESTHESIA, INTRAVENOUS/ or exp ADMINISTRATION, INTRAVENOUS/)

44 ((lidocaine* or xylocaine* or magnesium*) adj5 (intravenous* or IV*1)).ti. or ((lidocaine* or xylocaine* or magnesium*) adj3 (intravenous* or IV*1)).ab. or ((nonsteroidal or non-steroidal) adj3 anti-inflammatory adj3 (drug* or agent*)).ab.

45 or/39-44 [NSAIDs and locals]

46 11 and 45 [Ca + periop + (NSAIDs or locals)]

47 25 or 32 or 38 or 46

48 exp *BLOOD TRANSFUSION/ or BLOOD LOSS, SURGICAL/ or exp POSTOPERATIVE HEMORRHAGE/

49 ((transfus* and (blood* or erythrocyt* or leukocyt* or platelet* or plasma*)) or (blood and (loss or lost or losing or product*)) or (hemorrag* or haemorrag* or bleed* or hemosta* or hemodynamic* or haemosta* or haemodynamic*)).ti.

50 ((perioperativ* or peri-operativ* or intraoperativ* or intra-operativ* or pre-surg* or presurg* or post-surg* or postsurg* or preoperativ* or pre-operativ* or postoperativ* or post-operativ* or post-anesthe* or postanesthe* or post-anaesthe* or postanaesthe* or pre-anesthe* or preanesthe* or pre-anaesthe* or preanaesthe*) adj3 (transfus* or autotransfus* or auto-transfus* or hemorrag* or haemorrag* or bleed* or (blood adj3 (loss or lost or losing or product*)))).ab.

51 16 and 50 [adding #1 focus]

52 48 or 49 or 51 [transfusion/blood loss terms]

53 11 and 52 [Ca + periop + (transfusion or blood loss)]

54 BLOOD GLUCOSE/ or exp HYPERGLYCEMIA/ or exp HYPOGLYCEMIC AGENTS/ or GLUCOSE TOLERANCE TEST/ or HEMOGLOBIN A, GLYCOSYLATED/ or exp DIABETES MELLITUS/ or exp HYPERINSULINISM/ or exp INSULIN/

55 ((blood* adj3 glucose*) or euglycemi* or euglycaemi* or HbA1c or "Hb A1c" or "hemoglobin A1c" or diabet* or NIDDM or IDDM or T2DM).ti.

56 ((control* or manag* or treat* or monitor* or regulat* or regimen* or protocol*) and (glucose* or glycemi* or glycaemi* or insulin*1 or hyperglycemi* or hyperglycaemi*)).ti.

57 (((perioperativ* or peri-operativ* or intraoperativ* or intra-operativ* or pre-surg* or presurg* or post-surg* or postsurg* or preoperativ* or pre-operativ* or postoperativ* or post-operativ* or intraoperativ* or intra-operativ* or post-anesthe* or postanesthe* or post-anaesthe* or postanaesthe* or pre-anesthe* or preanesthe* or pre-anaesthe* or preanaesthe*) adj10 ((blood* adj3 glucose*) or euglycemi* or euglycaemi* or HbA1c or "Hb A1c" or "hemoglobin A1c" or diabet* or NIDDM or IDDM or T2DM)) or ((control* or manag* or treat* or monitor* or regulat* or regimen* or protocol*) adj5 (glucose* or glycemi* or glycaemi* or insulin*1 or hyperglycemi* or hyperglycaemi*))).ab.

58 or/54-57 [blood glucose terms]

59 11 and 58 [Ca + periop + blood glucose]

60 exp BODY TEMPERATURE/ or exp BODY TEMPERATURE CHANGES/ or exp HYPOTHERMIA, INDUCED/ or MALIGNANT HYPERTHERMIA/ or REWARMING/

61 ((body* adj3 temperature*) or sweat* or shiver* or fever* or hyperthermi* or hypothermi* or normothermi* or rewarm*).ti.

62 (((malignan* or anesthes* or anaesthes*) adj5 (hyperthermi* or hyperpyrexi*)) or (induc* adj5 hypothermi*)).ti.

63 ((body* adj3 temperature*) or sweat* or shiver* or fever* or hyperthermi* or hypothermi* or normothermi* or rewarm* or ((malignan* or anesthes* or anaesthes*) adj5 (hyperthermi* or hyperpyrexi*)) or (induc* adj5 hypothermi*)).ab.

64 or/60-62

Appendix continued

65 63 and (12 or 14) [ab kw + periop or anes focus]

66 64 or 65 [body temp terms]

67 11 and 66 [Ca + periop + body temp]

68 exp STEROIDS/ or GLUCOCORTICOIDS/

69 (corticosteroid* or glucocorticoid* or glucocorticosteroid* or steroid*).ti,rn.

70 (cortisone* or dexamethasone* or hydrocortisone* or methylprednisolone* or prednisolone* or prednisone*).ti,rn.

71 or/68-70 [steroid terms]

72 11 and 71 [Ca + periop + steroids]

73 (anesth* or analg* or anaesth* or pain*).in,jw. [anes term in author address or journal name]

74 11 and 73 [Ca + Periop + anes term in au addrs or jrnl name]

75 25 or 32 or 38 or 46 or 53 or 59 or 67 or 72 or 74

76 (animals not (humans and animals)).sh.

77 75 not 76 [removing "animal-only" studies]

78 (case reports not (case reports and review)).pt.

79 case report*.ti. not review.pt.

80 78 or 79 [case reports not part of a review]

81 77 not 80 [removing case reports unless part of a review]

82 exp CLINICAL TRIAL/ or exp CLINICAL TRIALS AS TOPIC/ or DRUG EVALUATION/ or exp EPIDEMIOLOGIC RESEARCH DESIGN/ or exp EPIDEMIOLOGIC STUDIES/ or COMPARATIVE EFFECTIVENESS RESEARCH/ [MeSH study terms]

83 81 and 82 [most likely CTs]

84 (randomized-controlled trial or rct* or multicenter study or controlled clinical trial or clinical trial or ((single or double or triple or treble) adj3 (blind* or dummy or mask*)) or ((random* or control* or clinical*) adj3 (study or studies or studied or trial*)) or ((multicent* or retrospective* or prospective*) adj3 (study or studies or studied or trial* or design*))).ti,ab.

85 81 and 84 [contain a CT term]

86 observational study.pt. or ((observ* or longitudinal* or open-label or cross-over or crossover or cross-section* or cohort* or comparative or comparison) adj3 (study or studies or studied or trial* or design*)).ti,ab.

87 81 and 86

88 comparative study.pt. or (case*1 adj3 series).ti,ab. or (drug* adj3 (compar* or evaluat*)).ti,ab. or "head-to-head".ti,ab. or (meta-analy* or met-analy*).ti,ab. or (meta-regression* or mega-regession*).ti,ab. or ((systematic* adj3 review*) or "systematic overview*").ti,ab. or ((methodologic* adj3 review*) or "methodologic* overview*").ti,ab. or (quantitative* adj3 (review* or synthes*)).ti,ab. or (research adj3 (integrat* or overview*)).ti,ab. or ((integrative* or collaborative*) adj3 (overview* or review*)).ti,ab. or (pool* adj3 analys*).ti,ab. or (data adj3 (synthes* or extract* or abstract*)).ti,ab.

89 81 and 88

90 81 and META-ANALYSIS/

91 limit 81 to systematic reviews [SR as publication type]

92 83 or 85 or 87 or 89 or 90 or 91

Medline (PubMed) – 2017 to November 13, 2018

1 Search "NEOPLASMS/surgery"[Mesh]

2 Search (cancer*[tiab] or neoplas*[tiab] or malignan*[tiab] or tumor*[tiab] or tumour*[tiab] or metasta*[tiab] or carcinoma*[tiab] or oncolog*[tiab] or recurrence*[tiab] or chemotherapy*[tiab] or chemo-therap*[tiab] or antineoplas*[tiab] or anti-neoplas*[tiab]) and (patient[tiab] or patients[tiab] or surg*[tiab] or resect*[tiab])

3 Search (cancer*[tiab] or neoplas*[tiab] or malignan*[tiab] or tumor*[tiab] or tumour*[tiab] or metasta*[tiab] or carcinoma*[tiab] or oncolog*[tiab] or recurrence*[tiab] or chemotherapy*[tiab] or chemo-therap*[tiab] or antineoplas*[tiab] or anti-neoplas*[tiab]) AND (patient[tiab] or patients[tiab] or surg*[tiab] or resect*[tiab])

4 Search #1 OR #2 OR #3

5 Search "PERIOPERATIVE PERIOD"[Mesh]

6 Search "PERIOPERATIVE CARE"[Mesh]

7 Search perioperativ*[tiab] or peri-operativ*[tiab] or intraoperativ*[tiab] or intra-operativ*[tiab]

Appendix continued

8	Search ((pre-surg*[tiab] or presurg*[tiab] or post-surg*[tiab] or postsurg*[tiab] or preoperativ*[tiab] or pre-operativ*[tiab] or postoperativ*[tiab] or post-operativ*[tiab]) and (anesthe*[tiab] or anaesthe*[tiab] or analges*[tiab] or block*[tiab] or post-anesthe*[tiab] or postanesthe*[tiab] or post-anaesthe*[tiab] or postanaesthe*[tiab] or pre-anesthe*[tiab] or preanesthe*[tiab] or pre-anaesthe*[tiab] or preanaesthe*[tiab] or "fast track"[tiab]))
9	Search #5 OR #6 OR #7 OR #8
10	Search #4 AND #9
11	Search "ANESTHESIA, INTRAVENOUS"[Mesh] and total[tiab]
12	Search "total intravenous anesthesia"[tiab] or "total intravenous anaesthesia"[tiab] or "total intravenous technique"[tiab]
13	Search tiva[tiab]
14	Search "HALOTHANE"[Mesh] or "ISOFLURANE"[Mesh] or "PROPOFOL"[Mesh]
15	Search (halothane*[tiab] or enflurane*[tiab] or isofulrane*[tiab] or sevoflurane*[tiab] or desflurane*[tiab] or propofol*[tiab])
16	Search (UQT9G45D1P[rn] or 91I69L5AY5[rn] or CYS9AKD70P[rn] or 38LVP0K73A[rn] or CRS35BZ94Q [rn] or YI7VU623SF[rn])
17	Search #11 OR #12 OR #13 OR #14 OR #15 OR #16
18	Search #10 AND #17
19	Search ("2017/05/01"[Date - Publication] : "3000"[Date - Publication])
20	Search #18 AND #19

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