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Review

Do Certain Anaesthetic Drugs Affect Postoperative Cancer Recurrence Rates? Implications for Drug Discovery

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Abstract: Recurrence of cancer after primary tumour resection is a leading cause of cancer-related mortality. Preclinical research indicates that surgery induces a stress response that inhibits cell-mediated immunity as a possible basis for risk of recurrence. Other preclinical evidence suggests that, conversely, propofol and local anaesthetics diminish the effects of the surgical stress response and so could directly inhibit cancer progression, and this is supported by several retrospective cohort studies and meta-analyses. However, the first large-scale randomised clinical trial (RCT), comparing recurrence after mastectomy in patients anaesthetised with either propofol/local anaesthetic or sevoflurane/opioids, concluded that recurrence was not significantly improved in the propofol/local anaesthetic group ($p = 0.84$). Other cancers may prove more responsive and results from a number of ongoing RCTs, encompassing several cancer types, are currently awaited. These trials should establish whether choice of anaesthetic technique is an important determinant of cancer recurrence risk.

Keywords: general anaesthesia; outcomes; mechanisms; cancer; perioperative medicine; clinical pharmacology

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1. Introduction

Surgical intervention is routinely employed as a potentially curative measure for many solid tumours, but post-operative recurrence of metastatic cancer is a limitation to improvements in outcomes. Surgery can directly contribute to metastasis and promotion of tumour growth though manual handling. Moreover, the surgical stress response (SSR), and its inhibitory effect on the immune system, are associated with oncogenesis [1]. Preclinical findings about the effects of different anaesthetics on the immune system, and more directly on the prevalence of recurrence, give rise to the proposition that local anaesthetics (LAs) [2] and propofol could limit recurrence (Figure 1) [3,4].

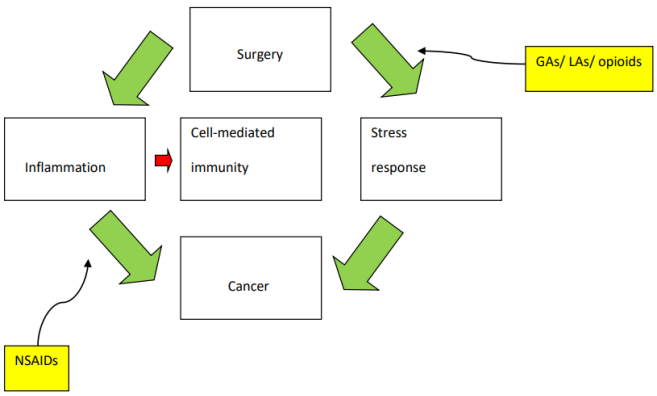

Figure 1. Outline of the effect of surgery (green lines) in promoting inflammation and a generalized surgical stress response that could in turn promote cancer recurrence; either directly or via inhibition

(red line) of cell-mediated immunity. Theoretically, drugs used in anaesthesia could inhibit this cancer recurrence pathway at several points: non-steroidal anti-inflammatory drugs (NSAIDs) at the inflammatory stage; or general anaesthetics (GA), local anaesthetics (LA) or opioids in obtunding the stress response.

Clinical study of this hypothesis has, so far, yielded no unanimous conclusions. However, the first large-scale clinical trial, recently published in *The Lancet*, determined that anaesthetic technique has no significant impact on recurrence following mastectomy [1]. It must now be established whether this study settles the issue or if further research is required.

2. Primary Tumour Resection and the Risk of Metastasis

Plasma concentration of inflammatory cytokines increases during surgery [2], remaining high up to 5 days post-operatively, depending on the degree of surgical insult [3]. Stress hormones (e.g., catecholamines and prostaglandins) are released during surgery as a result of sympathetic nervous system (SNS) and hypothalamic-pituitary-axis (HPA) signalling [4]. Dependent on the severity of the procedure, the SSR can last several days [5].

Cancer cells are released into circulation from the primary tumour handling during resection [6], establishing micro-metastases in non-affected tissues at sites remote from the primary tumour, where they can proliferate, develop their own blood supply, and ultimately form large metastatic tumours [7,8]. Thus, 59% of preoperatively asymptomatic breast cancer patients developed circulating tumour cells in the 22 years following mastectomy [9]. Cancer cell presence in plasma correlates strongly with increased risk of recurrence and poor long-term survival [10–12].

Surgery might also promote angiogenesis, through a hypoxia-inducible factor (HIF) pathway [13], driving metastatic tumour growth [14]. In a rabbit model of liver cancer, tumour blood flow after surgery increased alongside expression of the angiogenic proteins HIF-1α and related compounds [15]. Furthermore, study of human breast cancer patients after mastectomy has found that angiogenic gene expression increases and growth in distant metastases accelerates [16,17]. Additionally, the primary tumour can secrete both inhibitory and inductive agents, facilitating communication with disseminated cells [18]. Surgical resection disrupts the delicate balance of this control system, towards inductive signalling that could activate circulating tumour cells, promoting metastasis and recurrence [19]. Thus, endostatin and angiostatin concentrations decrease after surgery, while vascular growth and metabolic activity increase in metastases [15,20]. This implies that the primary tumour exercises inhibitory control over vascularisation of distant metastases, which is subdued following resection [21].

3. The Perioperative Period and the Immune System

The occurrence and survival of metastases is linked, intrinsically, to the immune system [20]. To understand how anaesthesia might affect recurrence, this relationship, and the impact of surgery on it, must be understood.

Cancer cells dampen the immune response by modulating the activity of immune cells [22]. Exacerbating inhibition of T, B and natural killer cells (NKCs) is commonly exhibited following surgery [2,23]. NKCs display a particularly potent level of anti-tumour activity and are thought essential in preventing spread and growth of metastases. NKCs are cytotoxic and through recognition of surface signals (e.g., lack of major histocompatibility, MHC, class-1 or the presence of a stress ligand) can selectively recognise and lyse cancer cells [24–26]. NKC inactivity correlates strongly with increased susceptibility to a wide range of cancers and the inhibitory effect of surgical stress on NKC activity is well documented in animals [27]. Surgery leads to reduced NKC activity and increased prevalence of metastases in mice; reversed by treatment with a prostaglandin synthesis inhibitor (indomethacin) and β-blocker (nadolol) [28]. Additionally, work in the MT/Ret mouse model showed that perioperative β-blockade (propranolol) delays primary tumour growth and metastasis development, while simultaneously increasing NKC infiltration

into the tumour stroma [29]. Increased expression of programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) by immune cells activates the PD-1 and PD-L1 pathways. These pathways increase caspase-3 activity which ultimately induces cell death/apoptosis, depleting the NK and T cell population. The level of expression correlates with the severity of surgical trauma [24,30].

T-helper lymphocytes, functionally divided into T_H1 and T_H2 subgroups, regulate cytokine expression. Generally, an abundance of T_H1 leads to stimulation of the immune system, while T_H2 is immunosuppressive [31]. Surgery shifts the ratio in favour of T_H2, leading to reduced levels of such immune-stimulating cytokines (termed IFN-γ, IL-2 and IL-12) and an increase in levels of immune-suppressive cytokines (e.g., IL-10 [31]). This shift towards T_H2 can plausibly promote postoperative growth in micro-metastases as cell-mediated immunity is suppressed.

4. General Anaesthesia: A Janus Effect?

Surgery for cancer cannot be dissociated from anaesthesia, and a wide range of agents are used in general anaesthesia. A combination of intravenous and inhalational agents induce and maintain unconsciousness. Analgesics include local anaesthetics, NSAIDs and opioids.

4.1. Evidence of Anaesthesia Promoting Cancer Recurrence

Some pre-clinical evidence suggests that volatile anesthetics inhibit cell-mediated immunity. In mice, both isoflurane and halothane inhibit NKC cytotoxicity and metastatic spread of melanoma can increase [32]. Isoflurane upregulates expression of the angiogenic and growth-promoting proteins HIF-1α, insulin-like growth factor-1, vascular endothelial growth factor (VEGF), angiopoietin-1, and other factors, increasing the malignant activity of ovarian cancer in-vitro [33,34]. Noting that volatile agents are commonly used in combination with nitrous oxide, N_2O, work in vitro found that sevoflurane increases expression of HIF-2α and key proteins in human head and neck squamous cell carcinoma; while N_2O disrupts DNA, purine and thymidylate synthesis and inhibits neutrophil chemotaxis, all of which suppress the response from tumour-surveying haematopoietic cells [35,36]. N_2O also significantly accelerates postoperative growth of lung and liver metastases in mice [37].

Intravenous agents were used historically to induce, rather than maintain anaesthesia (but see below). Some intravenous anaesthetics have, like the volatiles cited above, exhibited immune-suppressive properties in pre-clinical study. In human T lymphocytes in-vitro, thiopental inhibits activation of nuclear factor-kappa B (NF-κB) and neutrophil function. NF-κB suppression reduces activity of the NF-κB reporter gene which in turn limits expression of the important pro-immune factors (termed IL-2, IL-6, IL-8 and IFN-γ) [38]. Ketamine also inhibits expression of pro-immune IL-6, in addition to tumour necrosis factor-α, in-vitro [39]. Both agents have been shown to suppress NKC activity. Ketamine additionally induces apoptosis in T lymphocytes [39,40]. The action of thiopental is more protective against T lymphocyte apoptosis, suggesting complex interactions may be at play and all 'anaesthetics' cannot be regarded as equivalent [40].

4.2. Evidence of Anaesthesia Inhibiting Cancer Recurrence

Propofol appears to have the opposite effect, promoting aid cell-mediated immunity. Propofol increases cytotoxic T-lymphocyte activity and inhibits enzymatic production of inflammatory cytokines by cycolooxygenase-2 (COX-2) and the prostaglandin PGE_2 [41–43]. Melamed and colleagues tracked radiolabelled cancer cells in a rat model of breast cancer following administration of thiopental, ketamine and propofol. They found that thiopental and ketamine both significantly increased metastasis and tumour retention in the lungs 24 h after treatment, probably owing to reduced NKC activity. Propofol, in contrast, caused no such effect [44]. In vitro, propofol decreases survival in hepatocarcinoma, colorectal cancer, gastric cancer, lung cancer and glioblastoma cell lines via varying mechanisms [45–48]. Propofol also inhibits production of VEGF in-vitro, leading to suppression of angiogene-

sis [49]. If this effect were preserved clinically, as one comparative clinical trial of propofol and volatile anesthetics suggests, this might significantly limit tumour growth [50]. These preclinical studies are potentially important as propofol, in contrast to many other intravenous agents, is now administered as part of maintenance anaesthesis throughout surgery (the technique of 'total intravenous anaesthesia, TIVA), and not just as a single bolus dose for induction [51].

4.3. The Janus Effect: Analgesics

The Roman god Janus is depicted as having two faces looking in opposite directions. The summary of preclinical findings for general anaesthetic drugs above indicates potentially dichotomous effects, and this is also seen with opioids. On the one hand they are decidedly used to relieve pain and so obtund the stress response to surgery. Yet, some preclinical evidence suggests potential for promotion of cancer recurrence.

Morphine impedes NKC cytotoxicity with dose dependency in rats; and stimulates T_H2 activity and inhibits T cell differentiation in mice [52–54]. A study using human breast cancer xenografts concluded that morphine induces endothelial cell proliferation and angiogenesis (emulating VEGF by activating the mitogen-activated protein kinase signalling pathway and triggering extracellular signal-regulated kinase phosphorylation); inhibits apoptosis; and promotes cell cycle progression [54]. Fentanyl, sufentanil, remifentanil and alfentanil all suppress NKC activity in animal models [55]. Additionally, sufentanil inhibits leukocyte migration and remifentanil significantly impedes leukocyte proliferation in rats [56,57].

Overexpression of the μ-opioid receptor (MOR), due to cancer, may account for several pro-oncogenic side-effects of opioid treatment [58]. Histological analysis of lung tissue from patients with non-small cell lung carcinoma (NSCLC) revealed a 5 to 10-fold increase in MOR expression. In the same comprehensive study, Mathew and colleagues found that administration of morphine and enkephalin (MOR agonists) increases in vitro lung carcinoma growth. Meanwhile, treatment with the opioid antagonist methylnaltrexone or silencing of MOR expression reduces growth by 50–80%. Additionally, if injected with lung cancer cells, MOR-knockout mice develop no significant tumours compared with wild-type controls. Furthermore, chronic methylnaltrexone administration suppresses tumour growth and limits metastasis in mice injected with lung cancer cells [59]. In human non-small cell lung cancer cells, activation of MOR regulates opioid-induced growth factor receptor signaling, stimulating proliferation and migration of cancer cells. MOR activation may also promote pro-metastatic, epithelial-mesenchymal transition [60].

In contrast, animal studies indicate that higher doses of morphine do not promote tumour growth. Surgery-induced metastasis of mammary adenocarcinoma is blocked in rats administered high doses of morphine. An equivalent high dose had no effect on metastasis in non-operated rats [61]. Additionally, peri-operative, and in particular pre-operative, administration of morphine attenuated surgery-induced tumour growth in rats undergoing laparotomy [62]. It is important to note that a significantly higher dose of morphine is necessary to inhibit release of stress hormones than to induce analgesia [2,63]. Peri-operative administration of high-dose opioids may, therefore, be effective in diminishing the oncogenic effects of the SSR, despite the incidence of direct opioid-mediated suppression of immunity.

Non-steroidal anti-inflammatory drugs (NSAIDS) inhibit COX enzymes, impeding prostaglandin synthesis. Cancer cells express high levels of COX-2 and synthesise PGE_2, potentially as a mechanism of immune evasion [64]. PGE_2 is associated with promotion of cancer progression [65]. In animal models of cancer, COX-2 inhibitors attenuate angiogenesis; increase NKC cytotoxicity; and inhibit metastasis [66–69]. If administered after surgery, NSAIDS may also reverse some of the deleterious effects of surgical stress and treatment with opioids. An interesting study, using a murine model of breast cancer treated chronically with morphine, found the COX-2 inhibitor celocoxib inhibits opioid-induced angiogenesis, tumour growth and metastasis, improving survival while not compromising,

and potentially benefitting, analgesia [70]. Clinically, meta-analysis indicates that long-term use of NSAIDs could reduce both risk of developing cancer, and risk of metastasis in cancer patients [71,72]. A randomised clinical trial (RCT) into the effects of perioperative NSAID administration on recurrence is ongoing (NCT03172988).

In preclinical study, local anaesthetics appear to successfully suppress tumour growth and metastasis by modulating gene expression; inhibiting proliferation, migration and invasion; and are directly cytotoxic [73]. However, precise mechanisms have not yet been elucidated. Local anaesthetics work by inhibiting voltage gated sodium channels (VGSCs) thus disrupting neural nociceptive signal transmission. VGSCs are overexpressed in many cancer cells, which additionally express a range of ion channels not present in their terminally differentiated equivalents [74,75]. Importantly, continuous intravenous lidocaine infusion throughout surgery is now being promoted to aid analgesia, albeit with caution [75].

The local anaesthetic procaine demonstrates significant demethylating ability and can inhibit tumour cell proliferation by modulating cell-signalling pathways [76]. In lung cancer cell culture, procaine reactivates Wnt inhibitory factor-1 and down-regulates the Wnt canonical pathway (an important inhibitor of proliferation) [77]. Procaine also up-regulates expression of RASSF1A mRNA in nasopharyngeal carcinoma cells, inhibiting proliferation [78]. In vitro, ropivacaine, lidocaine and bupivacaine have all shown an antiproliferative effect on mesenchymal stem cells [79]. Epidermal growth factor receptor (EGFR) mutations are frequent in cancer cells [80]. EGFR, a tyrosine kinase receptor, is important in the epithelial cell proliferation pathway. Lidocaine can inhibit EGFR in tongue cancer (HT1080 fibrosarcoma). This inhibits proliferation by preventing shedding of heparin-binding epidermal growth-factor-like growth factor, which consequently cannot phosphorylate EGFR [81].

Tetracaine and lidocaine demonstrate an interesting ability to inhibit kinesin motility and protrusion of microtubules in breast cancer cells [82]. This inhibition hinders aggregation and reattachment, ultimately decreasing invasive ability and metastasis. A direct association has been shown between invasiveness of cancer and its relative VGSC activity, with greater expression of VGSCs exhibited in the most invasive ovarian cancer variants [83,84] Additionally, VGSCs appear to exercise control over VEGF signaling and other angiogenic functions in cultured umbilical vein endothelial cells [85]. A murine study found that peri-operative intravenous lidocaine reduces pulmonary metastasis after surgical resection with sevoflurane anaesthesia, likely by inhibiting expression of pro-inflammatory and angiogenic cytokines [86].

Administration of a clinically relevant dose of lidocaine or bupivacaine results in apoptosis of neuroblastoma, breast cancer, and thyroid cancer cells, [87–89] perhaps with sparing of healthy (mammary epithelial) cells. Apoptosis was triggered by induction of caspase-7, 8 and 9. Caspase-7 activity and evidence of apoptosis were also present in human breast cancer xenografts following local anaesthetic administration [88].

5. Evidence from Clinical Research

In summary, the pre-clinical evidence highlights propofol and local anaesthetics as the most promising agents to prevent cancer recurrence. The results from clinical research for these agents are mixed [90–104].

5.1. Propofol

Table 1 summarises some of the results of retrospective and prospective studies. It is not intended to be a meta-analysis (which are discussed below) but presented to reflect the inconsistency in results. In a large-scale study involving 7030 patients, encompassing several cancer types, volatile agents were associated with significantly lower survival after multivariable analysis [91]. This was corroborated in retrospective study of colorectal, gastric and liver cancer patients [97,100,102] However, the evidence does not unanimously support a beneficial effect for propofol. Several retrospective studies found no significant

difference in recurrence or survival between volatile and propofol groups. Furthermore, no significant benefit was shown in, small-scale, RCTs [92,103] A recent meta-analysis of 12 retrospective cohort studies found significant benefit to overall survival in TIVA groups (hazard ratio, HR = 0.73, 95% CI = 0.60–0.89) and improved, although not significant, recurrence-free survival with TIVA (HR = 0.73, 95% CI = 0.47 − 1.14) [104].

Table 1. Summary of some clinical studies comparing propofol (TIVA) vs. volatile-based anaesthesia in cancer recurrence. The second column of study type indicates whether the study is retrospective cohort (RC) or randomized control (RCT). The third column shows the numbers of patients in the propofol vs. volatile (VA) arms. The next columns indicate the agent used, the cancer type. The sixth column is the end point, being overall survival (OS); recurrence-free survival (RFS); tumour-node-metastasis stage (TNM); presence of metastasis (PM); biochemical recurrence (BCR), or not reported (nr). The last three columns indicate the hazard ratio, confidence intervals and rank (marked + for a 'positive' result or − for a 'negative' outcome indicating no effect on cancer recurrence).

Study	Study Type	Propofol/VA	Volatile Agent	Cancer Type	End Point	Hazard Ratio	95% CI	Result
Enlund et al. (2014) [90]	RC	1935/903	Sevoflurane	Various	OS	0.86	0.60–1.24	−
Wigmore et al. (2016) [91]	RC	3316/3714	Sevoflurane or isoflurane	Various	OS	0.68	0.60–0.78	+
Sofra et al. (2013) [92]	RCT	14/14	Sevoflurane	Bladder	OS	nr	nr, $p = 0.14$	−
Lee et al. (2016) [93]	RC	152/173	Sevoflurane	Breast	OS	nr	nr, $p = 0.38$	−
					RFS	0.48	0.27–0.86	+
Kim et al. (2017) [94]	RC	56/2589	Sevoflurane, isoflurane, enflurane or desflurane	Breast	OS	1.14	0.49–2.60	−
Yoo et al. (2019) [95]	RC	3085/2246	Sevoflurane, isoflurane, enflurane or desflurane	Breast	OS	0.96	0.69–1.33	−
					RFS	0.96	0.69–1.32	−
Huang et al. (2019) [96]	RC	344/632	Desflurane	Breast	OS	1.13	0.67–1.92	−
Wu et al. (2018) [97]	RC	657/706	Desflurane	Colorectal	OS	0.27	0.22–0.35	+
Oh Et al. (2016) [98]	RC	194/749	Sevoflurane	Non-small cell lung	OS	0.90	0.64–1.26	−
					RFS	1.31	0.84–2.04	−
Jun et al. (2017) [99]	RC	731/191	Sevoflurane, isoflurane or desflurane	Oesophageal	OS	0.63	0.50–0.81	+
					RFS	0.70	0.56–0.89	+
Zheng et al. (2018) [100]	RC	1506/1350	Sevoflurane	Gastric	OS	0.65	0.56–0.75	+
Dong et al. (2019) [101]	RC	154/140	Sevoflurane	Glioma	OS	nr	nr, $p = 0.76$	−
					OS (Low Karnofsky)	0.60	0.39–0.93	+

There are several factors to consider in interpreting these results. It is indeed interesting that retrospective studies point to some potential effect (i.e., elicit some 'signal' from the 'noise'). However, a true effect requires an RCT and even with randomisation it is not possible to even out potential patient factors that are more influential than the type of anaesthetic. Note also that, even with a volatile-based anaesthetic, bolus propofol is

invariably used for induction [105]. Study across a wider range of cancer types is warranted, because not all are identical in, for example, how they exhibit recurrence or the types of receptor targets they express. Finally, as a pragmatic observation, TIVA is currently used in less than 10% of all surgeries, in part because of concerns about other complications and side effects including accidental awareness during surgery [106].

5.2. Local Anaesthetics

Encouraging findings from early retrospective cohort studies have indicated that use of local anaesthetics during the peri-operative period could reduce incidence of cancer recurrence [107]. Table 2 summarises some of the results [108–143]. Like Table 1, this is not a meta-analysis and there are some important caveats to interpretation. Results from retrospective studies are inconsistent. A meta-analysis of 10 retrospective studies found that local anaesthesia during prostatectomy was associated with improved overall survival (HR = 0.81, 95% CI = 0.68 − 0.96) [144]. Similarly, a meta-analysis of 21 studies indicated that administration of neuraxial blockade (epidural or intrathecal) was associated with both longer recurrence-free survival (HR = 0.85, 95% CI = 0.72 − 1.0) and overall survival (HR-0.85, 95% CI = 0.74 − 0.98) [145]. However, another meta-analysis of 28 studies, found no association between local anaesthesia and improved survival or reduced recurrence [146]. As described previously, Sessler et al. determined that the combination of local anaesthesia and propofol (putatively the most promising combination) did not improve recurrence in breast cancer patients following mastectomy [1]. While this provides strong evidence that local anaesthetics are unlikely to improve breast cancer patient outcome specifically, this does not exclude the possibility, however remote, that other cancer types may respond more positively.

Table 2. Studies investigating recurrence following surgery with LA analgesia/anaesthesia or any opioid analgesia and general anaesthetic (GA). RC = retrospective cohort study; RCT = randomised clinical trial; OS = overall survival; RFS = recurrence free survival; TTR = time to recurrence; P/O = postoperative; I/O = intraoperative; SP = systemic progression; CSS = cancer specific survival; BCR = biochemical recurrence; PVB = paravertebral block; PCA = patient-controlled analgesia; IP = intraperitoneal; nr = not reported.

Study	Study Type	LA/Control	LA Technique	Control Technique	Cancer Type	End Point	Hazard Ratio	95% CI	Result
Sessler et al. (2019) [1]	RCT	1043/1065	LA PVB + propofol	Opioid + sevoflurane	Breast	RFS	0.97	0.74–1.28	–
Biki et al. (2008) [107]	RC	102/123	Epidural LA + GA	Opioid + GA	Prostate	BCR	0.43	0.22–0.83	+
Tsui et al. (2010) [108]	RCT	49/50	Epidural LA + GA	GA	Prostate	BCR	1.33	0.64–2.77	–
Wuethrich et al. (2010) [109]	RC	103/158	Epidural LA + GA	Opioid + NSAID + GA	Prostate	OS	0.61	0.29–1.28	–
						PFS	0.45	0.27–0.75	+
Forget et al. (2011) [110]	RC	578/533	Epidural LA + GA	GA	Prostate	BCR	0.84	0.52–1.17	–
Wuethrich et al. (2013) [111]	RC	67/81	Epidural LA + GA	Opioid + NSAID + GA	Prostate	OS	1.17	0.63–2.17	–
						Local RFS	1.16	0.41–3.29	–
						Distant RFS	0.56	0.26–1.25	–
Roiss et al. (2014) [112]	RC	3047/1725	Spinal LA + GA	GA	Prostate	OS	0.90	0.51–1.60	–
						RFS	1.11	0.54–2.27	–
						BCR	1.09	0.85–1.41	–
Sprung et al. (2014) [113]	RC	486/486	Epidural LA + GA	Opioid + GA	Prostate	OS	0.81	0.61–1.08	–
						RFS	1.27	0.96–1.67	–

Table 2. *Cont.*

Study	Study Type	LA/Control	LA Technique	Control Technique	Cancer Type	End Point	Hazard Ratio	95% CI	Result
Scavonetto et al. (2014) [114]	RC	1642/1642	Neuraxial LA + GA	GA	Prostate	OS	0.76	0.57–1.00	+
						SP	0.36	0.17–0.76	+
Tseng et al. (2014) [115]	RC	1166/798	Spinal LA + Sedative	GA	Prostate	BCR	0.91	0.70–1.18	–
Christopherson et al. (2008) [116]	RCT	85/92	Epidural LA + GA	GA	Colorectal	OS	1.43	0.75–2.70	–
Gottschalk et al. (2010) [117]	RC	256/253	Epidural LA + GA	GA	Colorectal	RFS	0.82	0.49–1.35	–
Gupta et al. (2011) [118]	RC	562/93	Epidural LA + GA	PCA + GA	Colorectal	OS (colon)	0.82	0.30–2.19	–
						OS (rectal)	0.45	0.22–0.90	+
Cummings et al. (2012) [119]	RC	9278/40377	Epidural LA + GA	GA	Colorectal	OS	0.91	0.87–0.94	+
						RFS	1.05	0.95–1.15	–
Day et al. (2012) [120]	RC	251/173	Epidural or Spinal LA + GA	PCA + GA	Colorectal	OS	Nr	nr, $p = 0.622$	–
Holler et al. (2013) [121]	RC	442/307	Epidural LA + GA	GA	Colorectal	OS	0.73	nr, $p < 0.002$	+
Vogelaar et al. (2015) [122]	RC	399/189	Epidural LA + GA	GA	Colorectal	OS	0.77	0.63–0.95	+
MacFater et al. (2020) [123]	RCT	37/19	IP LA + GA	IP Saline +GA	Colorectal	OS	0.65	nr, $p = 0.620$	–
Hiller etc. (2014) [124]	RC	97/43	Epidural LA + GA	GA	Gastric	OS	0.42	0.0.21–0.83	+
						TTR	0.33	0.17–0.63	+
Cummings et al. (2014) [125]	RC	766/1979	Epidural LA + GA	GA	Gastric	OS	0.93	0.84–1.03	–
Shin et al. (2017) [126]	RC	4325/374	Epidural PCA	i.v. PCA	Gastric	OS	0.67	0.43–1.13	–
						RFS	1.10	0.86–1.40	–
Wang et al. (2017) [127]	RC	1390/2856	Epidural LA + GA	GA	Gastric	OS	0.65	0.58–0.73	+
Li et al. (2016) [128]	RC	178/178	Epidural LA + GA	GA	Oesophageal	OS	Nr	nr, $p = 0.470$	–
						RFS	Nr	nr, $p = 0.460$	–
Lin et al. (2011) [129]	RC	106/37	Epidural LA + GA	Opioid + GA	Ovarian	OS	0.82	0.70–0.96	+
de Oliviera et al. (2011) [130]	RC	55/127	Epidural LA + GA	GA	Ovarian	P/O TTR	0.86	0.52–1.41	–
						I/O TTR	0.37	0.19–0.73	+
Capmas et al. (2012) [131]	RC	47/47	Epidural PCA + GA	GA	Ovarian	OS	1.25	0.39–4.04	–
						RFS	1.18	0.61–2.31	–
Lacassie et al. (2013) [132]	RC	37/43	Epidural LA + GA	GA	Ovarian	TTR	0.72	0.40–1.33	–
Tseng et al. (2018) [133]	RC	435/213	Epidural LA + GA	GA	Ovarian	OS	0.64	0.49–0.82	+
						RFS	0.75	0.60–0.94	+
Doiron et al. (2016) [134]	RC	887/741	Epidural LA + GA	GA	Bladder	OS	0.91	0.80–1.03	–
Weingarten et al. (2016) [135]	RC	195/195	Spinal LA + GA	GA	Bladder	OS	1.09	0.77–1.53	–
Choi et al. (2017) [136]	RC	718/158	Spinal LA	GA	Bladder	RFS	0.62	0.48–0.79	+
Koumpan et al. (2018) [137]	RC	135/96	Spinal LA	GA	Bladder	RFS	0.49	0.27–0.88	+
						TTR	0.64	0.46–0.88	+
Chipollini et al. (2018) [138]	RC	215/215	Epidural LA. + GA	GA	Bladder	RFS	1.67	1.14–2.45	–
						CSS	1.53	1.04–2.25	–
Zimmitti et al. (2016) [139]	RC	390/120	Epidural LA +GA	GA	Liver	OS	0.72	0.49–1.07	–
						RFS	0.74	0.56–0.95	+

Table 2. *Cont.*

Study	Study Type	LA/Control	LA Technique	Control Technique	Cancer Type	End Point	Hazard Ratio	95% CI	Result
Gottschalk et al. (2012) [140]	RC	52/221	Spinal LA	GA	Melanoma	OS	Nr	nr, $P = 0.087$	+
Merquiol et al. (2013) [141]	RC	111/160	Epidural LA + GA	Opioid + GA	Head and neck	OS	0.82	0.70–0.96	+
Myles et al. (2011) [142]	RCT	230/216	Epidural LA + GA	GA	Abdominal surgery (e.g., colorectal)	RFS	0.95	0.76–1.17	–
Wu et al. (2018) [143]	RC	1799/392	Epidural LA + GA	Opioid + GA	NSCLC	OS	0.81	0.58–1.31	–
						RFS	0.93	0.76–1.14	–

Table 2 reflects the caution that in all these studies, the local anaesthesia intervention is not equivalent. Paravertebral blocks are very different from epidural or intraperitoneal injection of local anaesthetic, and so on. Moreover, the plasma levels of local anaesthetic achieved with any of these are very low, so the only putative mechanism is through obtunding the stress response to surgery with analgesia.

6. Conclusions: Drug Development

The currently negative outcomes from RCTs do not support routine use of either propofol, local anaesthetic, or any other anaesthetic regimen as something to reduce risk of cancer recurrence. Studies may have failed to take account of several other perioperative factors, including blood transfusion and hypothermia, have been associated with increased recurrence [147–150]. Several large-scale RCTs are nearing completion that in part address these limitations (Table 3). However, an argument could also be made that if even these RCTs fail to demonstrate any positive results, then a time may come when research efforts and expense should be directed elsewhere rather than seeking marginal gains in this field of enquiry.

Table 3. Some ongoing registered clinical trials examining questions related to anaesthesia technique and cancer outcomes. The first column is the trial registration number; the second the study design; the third the target sample size; the fourth column is the comparison (TIVA, total intravenous anaesthesia; VA, volatile anaesthesia; LA, local anaesthesia; GA, general anaesthesia; PCA, patient-controlled analgesia). The fifth column shows the cancer type; the sixth column the end-points (OS, overall survival; RFS, recurrence-free survival). The last column indicates the planned/expected study completion date.

Study	Study Design	Participation	Agents	Cancer Type	End Point	Expected Completion Date
NCT03034096	Multicentre prospective	2000	Propofol TIVA vs. VA	Various	OS +RFS	December 2020
NCT01975064	Multicentre prospective	8000	Propofol TIVA vs. sevoflurane	Breast + Colorectal	OS	December 2023
NCT02786329	Single-centre prospective, 2×2 factorial	450	Propofol TIVA vs. VA and lidocaine vs. placebo	Colorectal	OS + RFS	December 2021
NCT02840227	Multicentre prospective	2000	Epidural LA + GA vs. opioid + GA	Non-small cell lung carcinoma	RFS	December 2021
NCT01318161	Single-centre prospective	300	Ropivacaine vs. morphine PCA	Colorectal	OS + RFS	December 2021

However, the preclinical evidence of beneficial properties of propofol and local anaesthetics with regard to cancer recurrence is more persuasive. While the dichotomy may be disappointing—interpreted for example as a failure in translating from bench to bedside—

in fact the preclinical data may guide drug discovery. General anaesthetics are chemically diverse, and it is increasingly appreciated that they work on a range of molecular target receptors. If their primary mechanism of action with respect to hypnosis is poorly understood, then it would seem more difficult to ascertain their mechanisms with respect to 'secondary' actions such as on cancer recurrence. Indeed, the notion of a 'common' mechanism of action for all agents is superceded by the theory that each agent produces unconsciousness in its own unique way [151]. Secondly, it is also being appreciated that, even for a given type of cancer (breast, prostate, etc), the surface cell markers and expression of relevant molecules or receptors may differ greatly across patients. Therefore, the positive results with preventing cancer recurrence may reveal, with further research, precisely which molecular targets are susceptible to the positive effects of general and/or local anaesthetics. In other words, the way forward may not be ever larger RCTs, in which the 'average' effect in a randomly sampled patient group is analysed; but, instead, more discrete analysis of which cancer subtypes (characterised by receptor expression) are amenable to beneficial effects of which anaesthetic agents.

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