Perioperative Intravenous Lidocaine and Metastatic Cancer Recurrence - A Narrative Review

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Cancer is a major global health problem and the second leading cause of death worldwide. When detected early, surgery provides a potentially curative intervention for many solid organ tumours. Unfortunately, cancer frequently recurs postoperatively. Evidence from laboratory and retrospective clinical studies suggests that the choice of anaesthetic and analgesic agents used perioperatively may influence the activity of residual cancer cells and thus affect subsequent recurrence risk. The amide local anaesthetic lidocaine has a well-established role in perioperative therapeutics, whether used systemically as an analgesic agent or in the provision of regional anaesthesia. Under laboratory conditions, lidocaine has been shown to inhibit cancer cell behaviour and exerts beneficial effects on components of the inflammatory and immune responses which are known to affect cancer biology. These findings raise the possibility that lidocaine administered perioperatively as a safe and inexpensive intravenous infusion may provide significant benefits in terms of long term cancer outcomes. However, despite the volume of promising laboratory data, robust prospective clinical evidence supporting beneficial anti-cancer effects of perioperative lidocaine treatment is lacking, although trials are planned to address this. This review provides a state of the art summary of the current knowledge base and recent advances regarding perioperative lidocaine therapy, its biological effects and influence on postoperative cancer outcomes.

Keywords: cancer, recurrence, anaesthesia, surgery, local anaesthetics, lidocaine

INTRODUCTION

The burden of cancer as a global health issue is enormous – with an estimated 18.1 million new cases and 9.6 million related deaths in 2018, it is the second leading cause of death worldwide (1). Although the discovery of new chemotherapeutic agents and radiotherapy techniques continues to promise significant results, surgery is the mainstay of treatment for the majority of solid tumours that are detected prior to metastasis. Indeed, over 80% of all patients diagnosed with cancer will undergo a surgical procedure of some nature, for diagnostic or therapeutic purposes, with approximately 45 million surgical procedures estimated to be required per year by 2030 (2). Unfortunately, and despite optimal care, cancer often recurs following intended curative surgery in
the form of metastatic disease. Metastatic cancer is typically refractory to treatment and is the most common cause of death in cancer patients (3). Therefore the importance of minimising recurrence risk is paramount. The physiological stress response induced by surgery stimulates inflammation and angiogenesis, eventually leading to fibrosis and wound healing. Paradoxically, these pro-inflammatory and pro-angiogenic stimuli also facilitate the survival and proliferation of residual cancer cells (4, 5). In recent years other perioperative events and conditions have been suspected of modifying the risk of metastatic disease development. Factors such as hypothermia, blood transfusion, and use of open (rather than minimally-invasive) surgical techniques are hypothesised as having detrimental effects on recurrence risk (6–8). Among these modifiable factors is the choice of anaesthetic and analgesic agents used perioperatively (9). A large volume of laboratory research has identified numerous pro- and anti-neoplastic effects associated with commonly used anaesthetic agents (10). Some retrospective clinical evidence has also pointed to a beneficial effect on cancer outcomes associated with the choice of anaesthetic used (e.g. intravenous agents such as propofol versus inhalational agents such as sevoflurane) (11, 12). There are multiple biologic pathways through which these agents may exert such effects, with modulation of the immune and inflammatory responses, as well as direct effects on cancer cells among the most likely candidates (13). The following sections will outline the perioperative use of lidocaine and our current understanding of the pathophysiology underlying postoperative cancer recurrence, before summarising recent laboratory, preclinical and clinical studies as well as planned trials examining lidocaine’s influence on cancer biology and outcomes.

**METHODS**

The keywords 'lidocaine cancer’ were used to search the Medical Literature Analysis and Retrieval System (MEDLINE), Excerpta Medica database (EMBASE) and Web of Science databases. Studies from 1 January 2000 until 10 March 2021 were included as well as any referenced articles deemed significant irrespective of publication date. Randomised controlled trials, retrospective studies, meta-analyses and systematic reviews were included. Articles were assessed for relevance and data were qualitatively analysed.

**PHYSICOCHEMICAL PROPERTIES OF LIDOCAINE AND CLINICAL USES**

Lidocaine (or 2-diethylaminoaceto-2′,6′xylidide, C14H22N2O) is the prototype amide local anaesthetic (LA) and clinically used both as an anaesthetic and analgesic agent, as well as an anti-arrhythmic. Lidocaine principally acts by blocking voltage-gated sodium channels, preventing the rapid influx of sodium required to depolarise the cell and thereby blocking neural impulse conduction. Hence, the transmission of pain signals from peripheral tissue to the central nervous system (CNS) is blocked (14). Lidocaine also possesses activity at a wide range of other ion channels and cell receptors which potentially contributes to its observed analgesic effects (15). Compared to the other amide LAs (e.g. bupivacaine), lidocaine has a shorter half-life and is less toxic - as a result, it is the only amide LA compatible with intravenous administration. Lidocaine toxicity manifests as CNS involvement (tinnitus, altered consciousness, seizures, coma) followed by cardiac signs (arrhythmias potentially resulting in cardiac arrest). Toxicity is rare when plasma concentrations are maintained below 5 µg.ml⁻¹ (~22µM) (16). In the perioperative setting, lidocaine is typically administered either systemically (intravenously) or to provide regional anaesthesia. Systemic lidocaine is given as an infusion during surgery (and often continued post-operatively) primarily for analgesic purposes; intravenous use has also been associated with faster return of gastrointestinal motility following bowel surgery, although evidence remains uncertain (17). One suggested regime consists of a maximum loading dose of 1.5 mg.kg⁻¹ followed by a maximal infusion rate of 1.5 mg.kg⁻¹.hr⁻¹ for up to 24 hours (18), although 2 mg.kg⁻¹.hr⁻¹ may achieve better analgesic effects (19). Resultant plasma concentrations are in the range of 0.5 – 5 µg.ml⁻¹ (2 – 22µM) (20).

**PATHOPHYSIOLOGIC BASIS OF POSTOPERATIVE CANCER RECURRENCE**

**Surgery, Circulating Tumour Cells and the Pre-Metastatic Niche**

Metastasis begins when cancer cells are liberated from the primary tumour, enter the lymphatics or bloodstream (forming circulating tumour cells, CTCs) and subsequently seed distant tissues. Intraoperatively, CTCs may inadvertently be created when cancer cells are dislodged during tumour manipulation (Figure 1). Even after CTCs deposit in remote tissues, much adversity has to be overcome to successfully endure hostile immune surveillance and inadequate local homeostatic supports. Cancers, however, possess a remarkable ability to precondition distant organs to form pre-metastatic niches (PMNs) to aid the future survival and proliferation of arriving CTCs (5). PMNs are pre-programmed by extracellular vesicles (EVs) released by the primary tumour - these are cell-derived, membranous structures containing proteins, lipids, messenger RNAs and microRNAs (21, 22). MicroRNAs in particular are potent contributors to PMN formation, allowing malignancies to achieve remote 'epigenetic regulation’ by altering gene expression in PMN cells to establish a pro-neoplastic milieu facilitating vascular permeability, angiogenesis and stromal degradation (5, 23, 24).

**Influence of Inflammation, Angiogenesis and the Surgical Stress Response on Cancer Progression**

Surgery may not only disseminate tumour cells - it further promotes cancer development via the surgical stress response,
inflammation and immunosuppression. Although vital for wound healing to occur, these physiological processes are strongly implicated in driving cancer progression; indeed, cancer has been called ‘a wound that does not heal’ (25). These processes may also cause previously formed micro-metastases to awake from dormancy and develop into significant metastatic disease. Thus excising cancerous tissue creates conditions which enhance the malignant potential of remaining cells (6).

**Inflammation**

Tissue injury creates an inflammatory state necessary to recruit and activate the cellular components responsible for wound healing (10). Macrophages and dendritic cells are activated and produce chemokines and pro-inflammatory cytokines including interleukins (such as IL-1, IL-1β, IL-6, IL-8, IL-12), tumour necrosis factor alpha (TNFα), and prostaglandins (26). Rapid increases in inflammatory mediators not only promotes local tissue healing but also stimulates cancer cell survival and proliferation (27). The immune system and the sensory nervous system (SNS) are tightly integrated: pro-inflammatory cytokines modulate pain transmission, causing peripheral and central pain sensitisation, increasing SNS and hypothalamic-pituitary-adrenal (HPA) axis outflow, in turn stimulating cytokine expression by immune cells (28). Expression of numerous signalling pathway elements are altered in the post-surgical inflammatory milieu, many of which are associated with cancer progression, including enzymes such as cyclo-oxygenase-2 (COX-2) and matrix-metalloproteinases (MMPs), and transcription factors such as nuclear factor kappa-beta (NF-κB) (29). Inflammatory cytokines impair endothelial integrity and endothelial function has been demonstrated to deteriorate for several days following surgery (30). Loss of endothelial function enables leucocyte transmigration and potentially facilitates the extravasation of CTCs into remote tissues (31). The tyrosine kinase enzyme Src contributes to this process via its actions as an important regulator of endothelial barrier integrity (32). Src is activated by inflammatory mediators, including TNFα, resulting in disruption of tight junctions between endothelial cells and eventual loss of endothelial function (32).

**Angiogenesis**

Surgical tissue injury causes localised tissue hypoxia, resulting in upregulation of hypoxia-inducible factor (HIF), in turn stimulating expression of vascular endothelial growth factor (VEGF). VEGF drives the synthesis of numerous tissue components involved in angiogenesis including integrins and extracellular matrix (33). Similarly, rapid growth of cancerous tissue creates a hypoxic cellular microenvironment, stimulating HIF and VEGF expression to create new blood vessels to supply the oxygen and nutrients necessary for further neoplastic
expansion. Overexpression of HIF and VEGF is associated with poorer prognosis in certain cancer types, including pancreatic and ovarian cancer (34, 35).

The Surgical Stress Response and Immunosuppression

The innate and adaptive components of the immune system act in unison to eliminate cancerous cells. Natural killer (NK) cells of the innate system, and T-cells (helper CD4+ Th1 cells and cytotoxic CD8+ T-cells) of the adaptive system provide cell-mediated immunity (CMI), the most important cellular anti-cancer immune response (36). This activity is influenced by post-operative pathophysiological changes - the initial inflammatory state is followed by a period of immunosuppression during which CMI is diminished (37). When the surgical stimulus activates the SNS and HPA axis, cortisol and catecholamines are released which inhibit the anti-tumour activity of NK cells and CD8+ T cells (6, 38). NK cytotoxicity is also reduced by increases in IL-6 and prostaglandin E2 (39). CMI is influenced by helper T-lymphocytes, which can be divided into two groups: Th1 cells favouring an anti-cancer CMI effect, and Th2 cells favouring antibody-mediated immunity (40). Post-operatively, Th2 proliferation increases, shifting the Th1/Th2 balance from a Th1-predominant CMI phenotype towards Th2 dominance, protecting cancer cells from immune attack (6).

Once considered relatively passive players, mounting evidence points to neutrophils having complex yet crucial roles in carcinogenesis (41). Circulating neutrophil counts are often increased by the post-operative inflammatory state, leading to an increased neutrophil-to-lymphocyte ratio (NLR) (42). NLR elevation is associated with poorer survival in some cancers – but whether this reflects causation or merely correlation is unclear (43). Circulating neutrophils can migrate into the tumour microenvironment where they adopt an anti- or pro-tumour phenotype, termed N1 and N2 respectively (44). N1 neutrophils phagocytose cancer cells whereas N2 neutrophils promote cancer in numerous ways, including reshaping stroma by expressing VEGF or MMP-9 (45). Neutrophils can also extrude condensed chromatin to form web-like structures called neutrophil extracellular traps (NETs) (46). This process (termed NETosis) is implicated in neoplasia with elevated serum markers of NETosis associated with poorer prognosis in certain cancers, and poorer post-operative outcomes in metastatic colorectal cancer (47, 48). How NETs promote metastasis is unclear - NETs may sequester CTCs without killing them, facilitating their arrest and possibly shielding them from cytotoxic immune cells (49, 50).

EXPERIMENTAL EVIDENCE OF LIDOCAINE’S ANTINEOPLASTIC EFFECTS

Lidocaine’s ability to inhibit cancer biology in vitro has been recognised for many years. Four decades ago, researchers identified that lidocaine exposure enhanced the cytotoxic effects of chemotherapeutic agents on cancer cells, with some authors attributing this phenomenon to inhibition of DNA damage repair (51). Since then, many cancers have been examined with numerous possible mechanisms of action proposed (52). To date, the accumulated evidence from many laboratory studies (Table 1) suggests that lidocaine possesses anti-neoplastic effects exerted via multiple biological pathways or components within cancer cells, and not just via voltage-gated sodium channels (31). In addition to direct effects on cancer cells, lidocaine also possesses anti-inflammatory properties which may modulate the pro-cancer effects of the stress response and preserve or enhance immune cell function (Figure 2) (82). Although in vitro studies are useful for establishing biological plausibility, their findings are not automatically transferrable to in vivo settings (83). Laboratory studies have often used human-toxic lidocaine concentrations, limiting the clinical applicability of their results. In addition, cancer in a host exists in a complex inter-relationship of cells, stroma, and cytokines, which is impossible to replicate in vitro. Lidocaine’s effect on cancer in vivo has historically been infrequently examined; however, results from several recent animal studies have supported the largely beneficial effects of lidocaine observed in vitro (Table 2).

EFFECTS ON CANCER CELL BIOLOGY

Effects on Bax/Bak/Bcl-2 and Apoptosis

Whether a damaged or pre-cancerous cell undergoes programmed cell death or not depends on the intracellular balance between pro- and anti-apoptotic mediators. The pro-apoptotic proteins, Bak and Bak, induce the mitochondrial release of cytochrome c and other apoptosis-regulating factors (94). These in turn activate caspases (proteolytic enzymes) which degrade cellular components causing cell fragmentation and phagocytosis by macrophages (94, 95). Countering Bak and Bak is the protein Bcl-2 which exerts anti-apoptotic effects favouring cell survival (96). Aberrant regulation of these pathways is linked to carcinogenesis. Lidocaine has been shown to induce apoptosis in multiple cancer cell lines in vitro across numerous studies (Table 1). Ye et al. observed that lidocaine inhibited gastric cancer cell proliferation, migration and invasion as well as promoting apoptosis – a finding associated with decreased Bcl-2 and increased Bax expression (62). Similar lidocaine-induced alterations in the Bax/Bcl-2 ratio to favour apoptosis were also detected in lung cancer cells (76). Separate studies examining osteosarcoma, thyroid cancer and hepatocellular carcinoma cells found that lidocaine-associated apoptosis was accompanied not only by alteration of the Bax/Bcl-2 ratio but also activation of caspases (80, 81, 93).

Effects on EGFR and the MAPK Pathway

The epidermal growth factor receptor (EGFR) is a widespread transmembrane receptor activated by a number of extracellular ligands including the mitogens EGF and TGF-α. Binding of ligands activates complex downstream signalling cascades, including mitogen-activated protein kinase (MAPK) systems such as the extracellular signal-regulated kinase (ERK1/2) and p38 pathways (97). This results in DNA transcription and
TABLE 1 | Selected in vitro studies examining the effects of lidocaine treatment on cancer cell biology.

| First author | Year | Cancer | Anti-neoplastic lidocaine effects detected | Proposed mechanism involved |
|--------------|------|--------|------------------------------------------|----------------------------|
| D’Agostino (63) | 2018 | Breast | Inhibition of cancer cell migration | Inhibited CXCL12/CXCR4 signalling |
| Li (64) | 2018 | Breast | Only high concentration (over toxic concentrations) of lidocaine inhibited affected cell viability or migration | Cancer cells arrested in S phase of cell cycle |
| Zhu (65) | 2019 | Cervical | Inhibition of cancer cell viability and promotion of apoptosis | Modulation of IncRNA-MEG3/miR-421/BTG1 signalling |
| Zhang (66) | 2019 | Choriocarcinoma | Lidocaine stimulates apoptosis in high concentrations, potentiation of the cytotoxicity of 5-FU | Reduction of ATP-binding cassette (ABC) transport protein expression |
| Qu (67) | 2018 | CRC | Inhibition of cancer cell proliferation and promotion of apoptosis | Suppression of EGFR expression by upregulation of microRNA miR-520a-3p |
| Siekmann (68) | 2019 | CRC | High concentration (1000µM) lidocaine reduced cell proliferation but low concentrations promote cell viability in metastatic cell lines | Not assessed |
| Tat (69) | 2019 | CRC | Reduced cell proliferation | Altered expression of caspase-8, HSP-27/60, IGF-II, IGF binding protein, p53, survivin |
| Bundschuh (70) | 2017 | CRC | Cell cycle arrest induced in two CRC cell lines by 1000µM lidocaine, but no change in cell proliferation noted | Cell cycle arrest |
| Zhu (71) | 2020 | Esophageal | Decreases cell growth, migration and survival | Causes mitochondrial dysfunction and oxidative damage, anti-migratory effects linked to decreased Rac1 activity |
| Ye (72) | 2019 | Gastric | Inhibition of cancer cell proliferation, migration, invasion and promotion of apoptosis | Decreased Bcl-2 expression, increased Bax expression, alteration of MAPK pathway |
| Sui (73) | 2019 | Gastric | Reduced cell viability, proliferation, migration and invasion, promoted apoptosis | Enhanced expression of miR-145, inactivation of MEK/ERK and NF-kB pathways, downregulated Bcl-2 expression, upregulated cleaved caspase-3/-7/-9 expression, decreased MMP-2/-9 |
| Yang (74) | 2018 | Gastric | Inhibition of cancer cell proliferation and migration | Down-regulation of p-ERK1/2 |
| Zhang (75) | 2020 | Gastric | Lidocaine inhibited cancer cell migration, as well as reducing resistance to cisplatin | Inhibition of B-catenin and AKT/mTOR pathways by decreased expression of miR-10b |
| Izedebisika (76) | 2019 | Glioma (rat) | Increased apoptosis and necrosis of cancer cells | Cytoskeletal reorganisation, possible induction of cytoprotective autophagy |
| Leng (77) | 2017 | Glioma (rat) | Lidocaine inhibits glioma cell proliferation | Inhibition of TRPM7 currents |
| Liu (78) | 2018 | Glioma (rat) | Reduced HCC cell viability and colony formation | Upregulation of cytoplasmic polyadenylation element binding protein 3 (CPEB3) |
| Jurj (79) | 2017 | HCC | Inhibition of cell proliferation | Reduced expression level of p53 |
| Le Gac (80) | 2017 | HCC | Lipidic acid decreased viability and proliferation of HCC cell, increased apoptosis of HCC progenitor cells | Increased mRNA of APC, an antagonist of the Wnt/B-catenin pathway |
| Ni (81) | 2018 | Leukaemia stem cells | Lipidic acid inhibited proliferation and colony formation of LSCs | Inhibition of Wnt/B-catenin signalling |
| Sun (82) | 2019 | Lung | Inhibited viability, migration, invasion; promotion of apoptosis | Increased expression of miR-539, inhibited EGFR signalling |
| Zhang (83) | 2017 | Lung | Reduced cancer cell proliferation | Downregulation of GOLTI1a expression |
| Yang (84) | 2019 | Lung | Lidocaine reduced cancer cell viability, migration and invasion, as well as reducing resistance of lung cancer cells to cisplatin | Down-regulation of miR-21 |
| Piegeler (85) | 2015 | Lung | Lipidic acid reduced cancer cell invasion | Lipidic acid reduced TNFα-induced activation of Akt, FAK, cavelin-1 and reduced MMP-9 secretion |
| Dong (86) | 2019 | Lung | Lipidic acid reduced viability of lung cancer cells | Increased Bax/Bcl expression, decreased Bcl-2 expression |
| Wang (87) | 2016 | Lung | Lipidic acid decreases viability, migration and invasion and promotes apoptosis in NSCLC cells | Downregulation of ΔΨm, provoked DNA damage, upregulated ROS production and activated MAPK pathways |
| Zheng (88) | 2020 | Melanoma | Lipidic acid inhibited migration and proliferation of melanoma cells and increased apoptosis | Inhibition of small GTPases RhoA, Rac1 and Ras |
| Wang (89) | 2017 | Melanoma | Lipidic acid sensitizes the cytotoxicity of 5-FU in melanoma cells | Upregulation of miR-493, potentially affecting SOX4-mediated pathways |
| Minshahidi (90) | 2020 | Osteosarcoma | Lipidic acid reduced viability of cancer cells, increased apoptosis | Bcl-2 and survivin expression decreased; Bax, cleaved caspase-3 and cleaved poly (ADP-ribose) polymerase-1 were increased |
| Chang (91) | 2014 | Thyroid | Decreases cell viability and colony formation, induces apoptosis | Activation of caspase 3/7, alters ratio of Bax/Bcl-2, attenuates ERK1/2 activity, activation of MAPK |

Promotion of processes leading to cell proliferation, migration and angiogenesis. MAPK pathways also play a role in apoptosis, where highly complex MAPK signalling may have either a pro-or anti-apoptotic effect depending on the cell type and stimulus involved (98). Defective EGFR signalling plays a major role in carcinogenesis, and many oncological therapies specifically target this signalling cascade (99). Lidocaine may also influence EGFR pathways resulting in antineoplastic effects. Researchers found that lidocaine increases expression of miR-539 (an EGFR suppressor) in lung cancer cells treated in vitro resulting in...
EGFR inhibition and reduced viability, migration and invasion as well as apoptosis (72). To reinforce these findings, the anti-neoplastic effects of lidocaine were attenuated when miR-539 was silenced (72). Another miRNA-based effect on EGFR was detected when the mechanisms by which lidocaine inhibited proliferation and enhanced apoptosis in colorectal cancer cells were examined (57). In this instance miR-520a-3p directly targeted EGFR and lidocaine increased its expression (albeit at 500-1000µM). Similar lidocaine-induced alteration of the miR-520a-3p/EGFR relationship leading to anti-neoplastic effects was also noted in retinoblastoma cells (92).

Alteration of p38 and ERK1/2 pathways have been hypothesised as underlying lidocaine’s anti-cancer effects in multiple in vitro experiments. In one study, lidocaine was noted to induce p38 phosphorylation in gastric cancer cells alongside an increase in apoptosis and decrease in proliferation, migration and invasion - the authors hypothesising that lidocaine-activated p38-MAPK signalling was the underlying mechanism (62). Other groups detected inactivation of both p38 and ERK1/2 pathways as well as activation of caspase 3 and alteration of the Bcl-2/BAX ratio when HCC cells were treated with lidocaine; in addition, viability was reduced and apoptosis increased in exposed cells (93). Further evidence linking anti-cancer effects of lidocaine to altered ERK signalling has been found in experiments examining gastric cancer, thyroid cancer and melanoma cells (64, 81, 90).

**Effects on NF-κB**

NF-κB is a protein transcription factor and regulator of numerous cellular processes occurring in response to tissue injury including immune response, inflammation, angiogenesis and apoptosis, in addition to playing a crucial role in cancer development (100). Cell stress signals (such as TNFα-receptor binding) are linked via intermediate steps to the translocation of the NF-κB complex into the cell nucleus whereupon transcription of potentially hundreds of target genes is activated or repressed (101). The exact nature of the resultant cellular response depends on complex, context-specific factors including cell type, cell health, and the nature of the stimulus. Adding to the complexity of NF-κB’s functions, multiple points of crosstalk exist between the NF-κB pathway and disparate signalling pathways involving transcription factors, microRNAs and cytokines, amongst others (100).
Dysregulation of Wnt pathways is associated with development of numerous malignancies including colorectal cancer (107). The protein known as adenomatous polyposis coli (APC) contributes to the formation of the β-catenin destruction complex which degrades β-catenin leading to reduced Wnt/β-catenin signalling thereby inhibiting cell proliferation and migration (108). Recent experimental evidence has suggested that lidocaine’s observed in vitro antineoplastic properties are potentially related to an effect on the Wnt/β-catenin pathway. One study identified that lidocaine increases the mRNA of the β-catenin antagonist APC ten-fold when applied to HCC cells, a finding associated with decreased cell viability and proliferation (70). Lidocaine repressed Wnt/β-catenin activity in two other in vitro studies examining gastric cancer and leukaemia cells respectively (65, 71). To the best of our knowledge, lidocaine’s effect on this pathway has yet to be examined in an animal model.

**Inhibition of Transient Receptor Potential Channels**

Transient receptor potential (TRP) channels are a large family of widely expressed membrane ion channels, playing a role in cell growth, survival and proliferation (109). Several TRP family members (including TRPV1, TRPV6 and TRPM7) have been associated with oncogenesis, and increased TRP expression correlates negatively with tumour grade and patient survival in some cancers (110). Lidocaine can inhibit TRPM7 channel current, and TRMP7 suppression is associated with reduced proliferation, migration and invasion of glioma and breast cancer cells in vitro (67, 111–113). Similarly, lidocaine reduced TRPV6 expression, migration and invasion in TRPV6-positive breast, prostate and ovarian cancer cells (114). Lidocaine also increased apoptosis in glioma cells, an effect attributed to activation of the TRPV1 gene (115).

**Inhibition of the Wnt/β-catenin Pathway**

Wnt pathways are complex signalling systems that direct cellular processes influencing organogenesis including cell fate determination, motility and stem cell renewal amongst others (106). β-catenin is a crucial component of the ‘canonical’ or Wnt/β-catenin pathway and acts as a transducer of this signalling mechanism which determines cell proliferation. Dysregulation of Wnt pathways is associated with development of numerous malignancies including colorectal cancer (107).
Effects on Src Signalling
Src is a non-receptor tyrosine kinase protein widespread in human cells and its encoding gene was the first proto-oncogene to be identified (116). Src is activated by various stimuli, such as TNFα binding to its receptor; activated Src phosphorylates a range of targets including the membrane protein caveolin-1. Src activation results in reduced endothelial barrier function and promotes cellular survival, proliferation, migration, invasion and angiogenesis (32, 117). Predictably then, activated Src in tumour cells is a potent oncogenic promoter and drives the pathogenesis of multiple cancers including colon, prostate and breast carcinomas (118, 119). Activated Src underpins lidocaine-related inhibition of pulmonary adhesion (121, 122). In a subsequent study, the same group showed that lidocaine-related inhibition of TNFα-induced, Src-dependent signalling in lung adenocarcinoma cells resulted in reduced MMP-9 expression and reduced cancer cell migration and invasion (120). Although Src inhibition by lidocaine on Src and associated signalling by-products have been studied both in vitro and in vivo. In separate experiments Piegeler et al. examined lung adenocarcinoma and lung endothelial cells in vitro and demonstrated that lidocaine not only inhibited TNFα-induced Src activation in both cell types, but also reduced cancer cell migration and endothelial cell permeability, as well as neutrophil adhesion (121, 122). In a subsequent study, the same group showed that lidocaine-related inhibition of TNFα-induced, Src-dependent signalling in lung adenocarcinoma cells resulted in reduced MMP-9 expression and reduced cancer cell invasion (75). Although Src inhibition by lidocaine has consistently demonstrated anti-tumour effects in vitro, this effect is yet to be confirmed in vivo. Our group examined whether an effect on Src underpinned lidocaine-related inhibition of pulmonary metastasis in a mouse model of breast cancer surgery by introducing an Src inhibitor alongside lidocaine. Although postoperative serum MMP-2 was reduced in lidocaine-treated animals, the results could not confirm an Src-dependent mechanism (86).

EFFECTS ON INFLAMMATORY CYTOKINE PRODUCTION
Lidocaine has long been known to possess anti-inflammatory properties (82). What has been more difficult to determine is the mechanism(s) by which inflammation is suppressed and the resulting clinical significance, if any. In vitro evidence from a number of studies has demonstrated that lidocaine inhibits release of leukotrienes, histamine and IL-1α from leukocytes - all potent inflammatory mediators (123, 124). Lidocaine may also inhibit the ‘priming’ or potentiation of neutrophil response to certain triggers of inflammation and thus reduce cytokine expression (125). In addition, lidocaine experimentally inhibits immune cell adhesion, migration and proliferation within areas of tissue injury (126). This may result from a protective effect of lidocaine on endothelium, preventing inflammatory mediator-induced injury and thus preserving endothelial barrier integrity (127). Conceptually then, perioperative lidocaine may inhibit immune cell infiltration into the pre-metastatic niche and prevent such cells releasing pro-metastatic inflammatory cytokines into this nascent tumour microenvironment, so reducing the risk of future metastasis development.

A number of small RCTs have examined the effect of i.v. lidocaine on post-operative cytokine expression (Table 3). Ortiz et al. randomised laparoscopic cholecystectomy patients (n=44)

### TABLE 3 | Selected RCTs comparing the effects of systemic lidocaine versus saline placebo on serum cytokine concentration.

| First Author | Year | Surgery Type & No. Recruited | I.V. Lidocaine Dosing | Effects on Postoperative Serum Inflammatory Marker Concentrations |
|--------------|------|------------------------------|----------------------|-----------------------------------------------------------------|
| Ortiz (128)  | 2016 | Laparoscopic cholecystectomy (n=44, 22 per group) | 1.5 mg.kg⁻¹ bolus then 3 mg.kg⁻¹.h⁻¹ until 1 hour post-surgery | IL-1, IL-6, IFN-γ, and TNFα reduced in i.v. lidocaine group and IL-10 increased compared with placebo group |
| Song (129)   | 2017 | Laparoscopic cholecystectomy (n=80, 40 per group) | 1.5 mg.kg⁻¹ bolus then 2 mg.kg⁻¹.h⁻¹ until end of surgery | IL-6 and IL-8 reduced in i.v. lidocaine group and no effect on IL-1ra compared with saline placebo |
| Kuo (130)    | 2006 | Colon cancer surgery (n=60, 30 per group) | 2 mg.kg⁻¹ bolus then 3 mg.kg⁻¹.h⁻¹ until end of surgery | IL-6, IL-8 and IL-1ra reduced by both i.v. and epidural lidocaine compared with saline placebo |
| Herroeder (131) | 2007 | Colorectal surgery (n=60, 30 per group) | 1.5 mg.kg⁻¹ bolus then 2 mg.kg⁻¹.h⁻¹ until 4 hours post-surgery | Lidoicaine attenuated increase of IL-6 and IL-8, no effect on IL-1β and TNF-α |
| Yardeni (132) | 2009 | Open hysterectomy (n=65, 32/33 in each group) | 2 mg.kg⁻¹ bolus then 1.5 mg.kg⁻¹.h⁻¹ until end of surgery | Lidoicaine attenuated the increase of IL-6 and IL-1ra produced by lipopolysaccharide-stimulated peripheral blood mononuclear cells |
| Srithar (133) | 2015 | Open abdominal surgery (n=134, 67 per group) | 2 mg.kg⁻¹ bolus then 1.5 mg.kg⁻¹.h⁻¹ until 1 hour post-surgery | Lidoicaine attenuated IL-6 compared to saline placebo |
| Dewinter (134) | 2017 | Spinal surgery (n=70, 35 per group) | 1.5 mg.kg⁻¹ bolus then 1.5 mg.kg⁻¹.h⁻¹ until 6 hours post-surgery | No significant differences between IL-6 and IL-1ra between the lidocaine and placebo groups |
| van den Heuvel (135) | 2020 | Breast cancer surgery (n=48, 24 received lidocaine) | 1.5 mg.kg⁻¹ bolus then 2 mg.kg⁻¹.h⁻¹ until 1 hour post-surgery | No effect attributed to lidocaine on serum IL-1β, IL-6, IL-10, IL-1ra |
| de Oliveira (136) | 2015 | Open hysterectomy (n=40, 20 per group) | No bolus, 2 mg.kg⁻¹.h⁻¹ infusion during surgery | No difference in serum IL-6 detected |
| Xu (137)     | 2021 | Laparoscopic hysterectomy (n=160, 4 groups of 40) | 1.5 mg.kg⁻¹ bolus then 1.5 mg.kg⁻¹.h⁻¹ until 30 mins before end of surgery | No difference in serum IL-1, IL-6 and TNF-α between control group receiving saline and group receiving lidocaine |
to receive either i.v. lidocaine (1.5 mg.kg⁻¹ bolus at surgical start then 3 mg.kg⁻¹.h⁻¹ until 1 hour after surgery) or i.v. saline as placebo (128). At 24 hours post-surgery compared to those receiving saline, i.v. lidocaine recipients had significantly reduced serum levels of pro-inflammatory cytokines (IL-1, IL-6, TNFα, IFN-γ) and an increase in the anti-inflammatory cytokine IL-10 suggestive of an overall anti-inflammatory effect. 5 other RCTs have detected that lidocaine has an inhibitory effect on serum cytokine concentrations following abdominal surgery, with IL-6 expression the most consistently suppressed; effects on clinical cancer outcomes were not assessed (129–133).

Not every RCT published to date has demonstrated lidocaine-related anti-inflammatory effects. Similar studies examining breast surgery, spinal surgery and hysterectomy patients found no difference in post-operative serum cytokines in their lidocaine treatment arms (134, 135, 137). There may be a number of reasons underlying the variable results observed in these trials. The enrolled numbers in the RCTs performed were small and most were powered to detect clinical outcomes (such as pain) as the primary outcome rather than cytokine changes. Significant heterogeneity existed not only in the dose and duration of infusion administered, but also in the time points at which cytokines were measured. Notably, all the RCTs reporting lidocaine-related cytokine reductions examined abdominal surgery, and indeed lidocaine’s clinical benefits in terms of analgesic effects, hastening return of bowel function and decreasing hospital stay appear most pronounced in this cohort (16).

EFFECTS ON ANGIOGENESIS

Given that inflammation and angiogenesis are often inextricably linked, it is difficult experimentally to isolate purely angiogenic pathways from inflammatory ones (138). There is significant overlap between the intracellular signalling pathways activated by both hypoxia and inflammation – hypoxia inducible factors (HIFs) increase transcription of NF-kB in the same way that inflammatory stimuli do, leading to amplification of inflammatory mediator production, as well as increasing expression of pro-angiogenic VEGF (138). The effects of lidocaine on HIF or VEGF specifically has infrequently been studied in laboratory or preclinical experiments. Gao et al. examined endothelial cells in vitro and found that VEGF-stimulated cell migration and proliferation was inhibited by lidocaine (50µM), as well as suppression of VEGF/VEGF receptor 2 (VEGFR2) signalling at 100µM (91). Using a mouse melanoma model, the same group found that intraperitoneal lidocaine treatment resulted in smaller tumours with reduced blood vessel formation. Separately, Suzuki et al. detected similar lidocaine-associated anti-angiogenic effects on endothelial cells in vitro although at lower concentrations (4 - 44µM), with similar suppression of VEGF/VEGFR2 signalling noted (139). In contrast, Nishi et al. reported that lidocaine (lowest concentration 30µM) did not affect hypoxia-induced HIF activation or alter expression of hypoxia-induced genes (140). Although choice of anaesthetic technique can alter post-operative serum VEGF in certain cohorts of cancer patients, the clinical significance of any such change is unknown and no definite effect on cancer outcomes has been proven (141, 142).

Only one RCT has examined the effect of systemic lidocaine on serum VEGF (though not as the primary outcome); breast cancer surgery patients (n=120) were randomised to anaesthesia using propofol or sevoflurane, with or without i.v. lidocaine – post-operative serum VEGF concentrations were unaffected by any treatment (143).

EFFECTS ON IMMUNE CELLS

The ability of some anaesthetic and analgesic agents to modify immune cell numbers and function is supported by laboratory evidence, although definitive clinical evidence of effects on patient outcomes is not confirmed (13, 38). Similarly, experimental evidence has accumulated indicating that lidocaine may modulate various cellular components of the immune system (31). As immune function and inflammation are closely associated, this effect may result from lidocaine’s anti-inflammatory properties as outlined previously. Or it may result from a direct action of lidocaine on immune cells, or indirectly via effects on SNS or HPA axis activity, or from some combination of these. Systemic lidocaine reduced circulating cortisol levels in parturients undergoing caesarean section in one trial, and post-operative urinary catecholamines in cholecystectomy patients in another (144, 145). Conversely, this effect was not observed in studies examining cortisol and/or catecholamine levels in colectomy or hysterectomy patients (146, 147). Based on this admittedly small body of evidence, SNS/HPA suppression cannot convincingly be identified as the primary means by which lidocaine influences immune cells.

Dendritic cells and macrophages treated with lidocaine in vitro express reduced amounts of inflammatory cytokines, a potentially beneficial anti-inflammatory and anti-cancer effect (148, 149). Conversely, lidocaine-related suppression of Th1 differentiation was detected both in vitro and in a mouse model, a potentially detrimental effect as Th1 cells contribute to cell mediated immunity (CMI). Clinically achievable concentrations of lidocaine may also benefit CMI by enhancing the cytotoxic effects of NK cells - in vitro NK cytotoxicity against leukaemia cells was promoted by lidocaine treatment (at 0.01µM to 50µM), an effect attributed experimentally to enhanced lytic granule release (150). Similar NK cytotoxicity enhancement was identified in a study which isolated NK cells from healthy donors and cancer patients (both pre- and post-operatively) - NK cells treated in vitro with lidocaine had greater cytotoxic effects against cancer cells (151).

A small RCT randomised 30 patients undergoing radical hysterectomy to i.v. lidocaine (1.5 mg.kg⁻¹ bolus then 1.5 mg.kg⁻¹.h⁻¹ during surgery) or saline (152). Lidocaine treatment preserved post-operative lymphocyte proliferation and inhibited apoptosis. Another RCT, again involving
hysterectomy patients (n=65), randomised subjects to i.v. lidocaine (2 mg.kg\(^{-1}\) bolus then 2 mg.kg\(^{-1}\).h\(^{-1}\) during surgery) or saline (132). Again an immune protective effect was detected - lidocaine attenuated suppression of the lymphocyte proliferative response, in addition to inhibiting expression of IL-6 and IL-1ra. Not all clinical studies have demonstrated beneficial immune effects - i.v. lidocaine (1 mg.kg\(^{-1}\) bolus) in patients with herpes zoster-related pain did not affect NK numbers or activity (153).

Lidocaine inhibits neutrophil adhesion and migration \textit{in vitro}, with effects on the integrin member CD11b-CD18 or the Nav1.3 voltage-gated sodium channel among the mechanisms postulated (154, 155). Evidence of lidocaine’s effects on neutrophils has also been established by several animal and human studies. One \textit{in vivo} study found that lidocaine (administered intra-peritoneally in a mouse peritonitis model) inhibited neutrophil apoptosis and macrophage clearance and delayed the resolution of the inflammatory response and return to normal homeostasis (156). Systemic lidocaine also inhibited leukocyte accumulation in animal models of peritonitis and myocardial ischaemia (157, 158). Clinical evidence is limited – in an RCT conducted by Berger et al., intravenous lidocaine administered to septic patients reduced chemokine-induced adhesion and transmigration of neutrophils through endothelium without affecting expression of adhesion molecules (159).

Lidocaine has long been recognised as affecting neutrophil phagocytic function (160), although accumulated evidence appears contradictory as to whether function is enhanced or impaired. Kawasaki et al. treated human neutrophils with lidocaine (at supraclinical 400µM) \textit{in vitro} and found respiratory burst and phagocytic ability were impaired (161). Similar effects on respiratory burst have also been reported in neutrophils isolated from umbilical cord blood from newborns and treated \textit{in vitro} with high concentration lidocaine (4mM), whereas low concentrations (2µM) appeared to increase reactive oxygen species production (162). However, other groups did not detect any lidocaine-related effect on \textit{in vitro} neutrophil function or reactive oxygen species production when clinically achievable concentrations were tested (163–165). One clinical study examining neutrophils taken from lidocaine-treated patients detected significantly reduced superoxide anion release compared to patients who didn’t receive lidocaine (166). Contrary to this finding, a clinical trial studying bolus lidocaine (1.5 mg.kg\(^{-1}\)) administered at induction of anaesthesia found that lidocaine actually preserved neutrophil respiratory burst compared to neutrophils from control patients who received saline (167).

The choice of anaesthetic technique can modulate the neutrophil-to-lymphocyte ratio (NLR) post-operatively, however significant effects on clinical outcomes are not proven (168, 169). Evidence from one small RCT also suggests beneficial effects of lidocaine on post-operative NLR following breast cancer surgery although, again, clinical outcomes were not assessed (170). Unsurprisingly given the relatively recent discovery of the phenomenon of NETosis, it has infrequently been studied in the context of cancer surgery. However, one RCT found that i.v. lidocaine reduced serum biomarkers of NETosis (namely neutrophil myeloperoxidase and citrullinated histone H3) after breast cancer surgery (143).

**PRECLINICAL STUDIES OF CANCER OUTCOMES**

Although to date far fewer preclinical studies have been conducted than laboratory experiments, a number of animal studies have identified beneficial effects of lidocaine on \textit{in vivo} cancer growth and outcomes (Table 2). Chamaraux- Tran et al. injected immunodeficient mice intraperitoneally with human breast cancer cells, randomised the animals to weekly intraperitoneal lidocaine or saline treatment, and demonstrated that lidocaine treatment significantly improved survival and reduced tumour growth (84). Similarly, lidocaine treatment has been proven to reduce tumour size and improve survival when administered intravesically alongside mitomycin C in a mouse model of bladder cancer (85). Lidocaine also decreased tumour size when administered intraperitoneally in mouse models of melanoma and hepatocellular carcinoma, and intravenously in models of melanoma and retinoblastoma (90–93). We previously established a syngeneic mouse breast cancer model to mimic the effects of anaesthesia and surgery on postoperative metastatic progression (87). In this model, animals that received an intravenous lidocaine infusion alongside sevoflurane anaesthesia during resection of primary breast tumours had consistently fewer pulmonary metastases when measured two weeks postoperatively (86, 88, 89).

**CLINICAL STUDIES OF CANCER OUTCOMES**

Following reports from retrospective analyses suggesting decreased cancer recurrence rates associated with regional anaesthetic techniques in breast and prostate cancer surgery, there has been an increased focus on establishing which anaesthetic technique, if any, provides the greatest outcome benefit following surgery (171, 172). Evidence accumulated from laboratory and retrospective clinical studies suggests that intravenous (i.e. propofol-based) and regional anaesthesia are potentially beneficial in terms of effects on cancer outcomes compared to volatile anaesthesia and opioids (10). However, the first large RCT examining this topic, which randomised breast cancer surgery patients to a propofol-regional anaesthesia technique versus a volatile-opioid technique, found no difference in recurrence rates between the two groups (173). Given the huge degree of biological heterogeneity between different malignancies, it is difficult to determine how applicable these findings may be to other cancer surgery types e.g. colorectal cancer surgery. Other trials currently underway, assessing anaesthetic technique and cancer outcomes across a range of different cancer types, will go some way towards addressing this uncertainty.
Although numerous studies have examined the effects of intravenous lidocaine on biochemical or haematological markers of inflammation, angiogenesis and immune function, to the best of our knowledge, only one study to date has reported on clinical outcomes. Zhang et al. in a recent retrospective study of 2239 patients undergoing resection of pancreatic carcinomas found that those who received perioperative i.v. lidocaine (1.5 mg.kg⁻¹ bolus followed by 1.5 mg.kg⁻¹.hr⁻¹) had significantly better overall survival at 1 and 3 years (68.0% vs 62.6%, p=0.001; 34.1% vs 27.2%, p=0.011), although disease-free survival was unaffected (174).

**FUTURE RCTs - ESTABLISHING SYSTEMIC LIDOCAINE’S EFFECT ON CANCER OUTCOMES**

The question of whether perioperative systemic lidocaine has any influence on postoperative cancer outcomes can only be answered by the completion of a suitably powered RCT. No such trial has ever been completed, which is understandable considering the cost, patient number and length of follow up required. However, this question will be addressed for a subset of cancers by the Volatile Anaesthesia and Perioperative Outcomes Related to Cancer trial (VAPOR-C, NCT04316013) which is planned to complete in 2025. VAPOR-C will recruit 5736 colorectal and lung cancer patients and in a 2x2 factorial study randomise them to either sevoflurane or propofol anaesthesia, plus lidocaine infusion (1.5 mg.kg⁻¹ bolus followed by 2 mg.kg⁻¹.hr⁻¹ for 4 hours then 1.5 mg.kg⁻¹.hr⁻¹ thereafter) or saline placebo (175). The primary outcome measure will be disease-free survival, with overall survival as a secondary endpoint.

The ALLEGRO RCT (ISRCTN52352431), which is currently ongoing and aims to recruit 562 patients, is examining the effect of systemic lidocaine (1.5 mg.kg⁻¹ bolus followed by 1.5 mg.kg⁻¹.hr⁻¹ for 6 or 12 hours) during colorectal surgery on post-operative bowel function. Cancer outcomes will be also be studied up to 10 years post enrolment, although these are tertiary endpoints so will likely be underpowered but will potentially be a useful addition to the knowledge base (176). Other small trials are examining perioperative systemic lidocaine and cancer outcomes in colorectal surgery (NCT02786329) and pancreatic surgery (NCT04449289).

**LICENCING AND SAFETY CONCERNS**

The appropriateness of intravenous use of lidocaine given the potential risks and as yet inconclusive benefits has recently been questioned (177). Lidocaine remains unlicensed for intravenous use for analgesic purposes, although many drugs used routinely in anaesthesia are similarly used in an ‘off-label’ manner. The likelihood of encountering toxicity appears very small when carefully dosed and under continuous monitoring, with one surgical unit reporting over 2200 patients treated with perioperative i.v. lidocaine with no reported adverse effects (20). Despite this, the potential for toxicity can never be completely excluded and therefore the potential risks and benefits of systemic lidocaine should be carefully considered by the practitioner for each patient prior to commencing treatment. Recently published dosage guidelines may aid in ensuring safe practice, with dosages reduced accordingly (or usage avoided) in the presence of conditions known to enhance toxicity (18). In addition, as recently proposed, adoption of institutional guidelines regarding administration, monitoring, detection and treatment of systemic toxicity appears prudent wherever i.v. lidocaine is administered, and training of all involved staff should be mandatory (178). Perhaps, as recently suggested by Pandit and McGuire, use of intravenous lidocaine is currently best confined to subjects participating in clinical trials (including VAPOR-C) under rigorous safety conditions and where the results of usage can contribute to establishing definitive evidence of clinical benefits or otherwise (179).

**CONCLUSION**

The cancer patient’s perioperative course is increasingly recognised as a period during which future malignant progression may be influenced for better or worse. Cancer progression appears dependent on the development of a harmful imbalance between pro- and anti-neoplastic humoral and cellular effects, in favour of the malignancy. Circulating tumour cells released by dissection, which under normal conditions would be eradicated by the immune surveillance system, may instead establish themselves in pre-metastatic niches in distant organs, where their survival is facilitated by the pathophysiological effects generated by the surgical insult. Or pre-established micro-metastatic deposits may be woken from their dormancy in the tumour microenvironment by the same processes. Any intervention made during this critical time which can rebalance these systems in favour of host survival holds tremendous promise for improving patient outcomes. Lidocaine has been shown experimentally to possess numerous beneficial effects, potentially affecting multiple biological pathways to act as an anti-inflammatory, immune cell modulator and/or direct inhibitor of cancer cells. An intravenous infusion of lidocaine administered perioperatively may act as a simple, inexpensive and effective chemotherapeutic agent in addition to its potential analgesic properties. Only evidence from adequately powered, randomised, controlled clinical trials will confirm lidocaine’s efficacy in improving cancer outcomes - the planned VAPOR-C trial should go some way towards establishing this.

**AUTHOR CONTRIBUTIONS**

Conceptualization: TW and DB. Writing – Original Draft Preparation: TW and DB. Writing – Review & Editing: TW and DB. All authors contributed to the article and approved the submitted version.
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