Direct Cytotoxic and Indirect, Immune-Mediated Effects of Local Anesthetics Against Cancer

Alejandra Wu Chuang1,2, Oliver Kepp1,2, Guido Kroemer1,2,3* and Lucillia Bezu1,2,4*

1 Equipe Labellisée Par La Ligue Contre Le Cancer, Université de Paris, Sorbonne Université, INSERM UMR1138, Centre de Recherche des Cordeliers, Paris, France, 2 Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Université Paris Saclay, Villejuif, France, 3 Pôle de Biologie, Hôtel européen Georges Pompidou, AP-HP, Paris, France,
4 Service d’anesthésie, Gustave Roussy Cancer Campus, Villejuif, France

Local anesthetics are frequently employed during surgery in order to control peri- and postoperative pain. Retrospective studies have revealed an unexpected correlation between increased long-term survival and the use of local anesthetics during oncological surgery. This effect of local anesthetics might rely on direct cytotoxic effects on malignant cells or on indirect, immune-mediated effects. It is tempting to speculate, yet needs to be formally proven, that the combination of local anesthetics with oncological surgery and conventional anticancer therapy would offer an opportunity to control residual cancer cells. This review summarizes findings from fundamental research together with clinical data on the use of local anesthetics as anticancer standalone drugs or their combination with conventional treatments. We suggest that a better comprehension of the anticancer effects of local anesthetics at the preclinical and clinical levels may broadly improve the surgical treatment of cancer.

Keywords: local anesthetics, immunity, cancer, cell death, surgery

INTRODUCTION

Malignant disease remains the second cause of death worldwide. According to the World Health Organization, cancers were responsible for 10 million deaths in 2020 (1). In most cases, treatment of solid cancers relies on tumor removal by surgical excision combined with conventional therapies such as chemotherapy and radiotherapy (2). However, standard oncological surgery may promote recurrence by facilitating cancer cell dissemination due to the mechanical removal of the tumor accompanied by the stimulation of vascular endothelial growth factor (VEGF) production by the surrounding tissue (3). Moreover, surgery often induces a stress response composed of organismal metabolic changes, local inflammation and pain, thus causing an elevation of circulating...
Local Anesthetics Induce Cancer Cell Death

Wu Chuang et al.

Local Anesthetics Possess Direct Antitumoral Activities

Local Anesthetics Counteract Tumor Cell Migration

LAs such as lidocaine, ropivacaine, levobupivacaine, bupivacaine, procaine or chloroprocaine are used in clinical practice for their analgesic properties, which are explained by the blockade of voltage-gated sodium channels necessary for pain nerve conduction (19). Surprisingly, many observational retrospective studies reported an improved overall survival after the use of local anesthetics (LAs) employed alone or in combination with general anesthesia during solid tumor resection. Thus, as compared to general anesthesia alone, the combination of epidural and general anesthesia, which is usually performed to relieve major surgery-induced pain, was associated with a better long-term survival after abdominal and gynecological debulking (8–11). An enhancement of clinical progression-free time was also noticed after regional anesthesia after prostate, liver or breast primary tumor removal (12–14). Despite supplemental meta-analyses strengthening these positive outcomes, no guidelines emerged from these studies given their limits and weaknesses (15–18). However, rational hypotheses to explain these observations appeared in the literature, supporting the possibility of novel guidelines in oncological anesthesia. Here we aim at discussing the main signaling pathways underlying the antitumor effect of local anesthetics. For this, we summarize published fundamental and clinical research while focusing on the mechanisms through which the immune system is activated by local anesthetics. We specifically dwell on their capacity to potentiate conventional antineoplastic therapies, hoping to improve clinical praxis in this area of oncology.

Figure 1: Local anesthetics influence immune cell function and tumor cell migration. LAs such as ropivacaine and bupivacaine increase the expression of CXCR4 and downregulate the expression of CXCR1 in human umbilical vein endothelial cells (HUVECs), thereby inhibiting the migration of cancer cells (25). The anti-invasive property at concentrations lower than those used in clinical practice (<1mM) (21, 25). We may hypothesize that low plasma concentrations of LAs from patients receiving local or from human fibrosarcoma cells and by modulating intracellular Ca²⁺ (22). Ropivacaine was also described to increase E-cadherin protein expression and to downregulate vimentin, which is a major intermediate filament, thus contributing to reduce metastases (23). Note that tetracaine inhibits the formation of tubulin microtentsacles that are required to promote reattachment of detached breast tumor cells during metastatic dissemination (24). Taken together, these findings indicate the existence of multiple molecular mechanisms by which LAs inhibit cancer cell dissemination. It is important to point out that, despite the presence of voltage-gated sodium channels on various cancer types such as breast, colon and lung tumor cells, most of the LA-induced anti-metastatic processes may be ascribed to mechanisms that do not require the inhibition of voltage-gated sodium-channels (22, 25–27) Figure 1.

In addition, bupivacaine, procaine and ropivacaine are endowed with the capacity to minimize the migration of neoplastic cells by inhibiting mitochondrial function. Indeed, due to their capacity to block signaling pathways operating downstream of RhoA such as the ROCK/MLC, ERK/MAPK/FAK and Rac1/JNK/paxillin/FAK pathways that commonly lead to apoptosis, local anesthetics inhibit the migration of cancer cells (25–28).

A non-negligible role of microRNAs in cancer regulation and cells migration was suggested in different models of solid cancers treated by LAs. Thus, ropivacaine enhances miR-202a-3p expression in gastric cancer cells, thereby inactivating WEE1 and PI3K/AKT signaling and inhibiting cell migration (29). Lidocaine showed an unexpected ability to up-regulate miR-145 and miR-539 expression in gastric carcinoma MKN45 cells and in lung cancer cells, respectively. These microRNAs directly downregulate epithelial growth factor receptor (EGFR), which is a prominent target for anticancer drugs and plays a major role in tumorigenesis and cancer cell invasion (30, 31). In addition, procaine induces similar antiproliferative effects by up-regulating miR-133 (32).

At clinically relevant concentrations, both lidocaine and ropivacaine block cell invasion. LAs interact with the secretion of matrix metalloproteinases (MMP) such as MMP-2 and with tumor necrosis factor (TNF) α-dependent MMP-9 involved in invasion process by inhibiting Src-dependent inflammatory signaling pathways (33, 34). This anti-inflammatory effect does not result from direct effects on the cytoskeleton but rather from the capacity of LAs to block cancer cell migration secondary to their anti-inflammatory properties. Indeed, Src protein tyrosine kinase plays a key role in the homeostasis of the endothelial barrier. Its activation by phosphorylation is induced in response to inflammation. Furthermore, surgical procedures provoke acute inflammatory process including vasodilatation, edema and loss of endothelial barrier integrity, thereby facilitating transmigration, extravasation and dissemination of tumor cells through lymphatic and vascular circulation Figure 1.

Interestingly, some LAs (lidocaine and bupivacaine) elicit an anti-invasive property at concentrations lower than those used in clinical practice (<1mM) (21, 25). We may hypothesize that low plasma concentrations of LAs from patients receiving local or
regional injection of LAs could suffice to exert systemic effects on residual cancer cells, stopping their migration.

Finally, in models of tumor resection established in immunocompetent mice that have developed syngeneic transplantable EL4 lymphomas or 4T1 breast cancers, lidocaine and bupivacaine used alone or combined with general anesthesia significantly decreased spontaneous metastasis independently of the route of administration (intravenous, spinal block or local infiltration of the inoculation site) (35–38). The mechanisms accounting for these antimetastatic effects remain unclear. However, an LA-induced reduction of circulating MMP-2 levels might contribute to impair tumor cell migration (38).

**Local Anesthetics Inhibit Tumor Cell Proliferation**

LAs are able to stop tumor cell proliferation as indicated by the decrease in the mitotic marker Ki-67 as well as by a cell cycle arrest (39, 40). Most of the published data showed that this effect is concentration and time dependent (41–43). Many mechanisms may explain this process. LAs directly interfere with the advancement of the cell cycle by reducing cyclins (A2, B1, B2, D, E) and cyclin-dependent kinases expression in various models of human solid cancers (colon, lung, melanoma, thyroid, liver, breast) (28, 34, 39, 44–47). In addition, LAs induce mitochondrial dysfunction causing inhibition of respiratory chain activity and ATP production as well as a shutdown of glycolysis. This LA-induced disruption leads to mitochondrial membrane depolarization, the release of cytochrome c into the cytosol favoring the activation of apoptotic caspases, as well as cell damage mediated by reactive oxygen species (ROS) (48–51). Some LAs affect the DNA methylation status by modulating DNA methyltransferases (DNMT) activation in several types of cancer cell lines. The decrease in global methylation induced by LAs may restore the expression of previously silenced tumor suppressor genes and mediate growth-inhibitory effects on cancer cells (40, 52–58). Furthermore, some experiments suggest the implication of microRNAs in the inhibition of cancer cell proliferation (23, 29, 59). Finally, in a model of human colorectal cancer, bupivacaine and its levorotatory enantiomer levobupivacaine promote the expression of C/EBP
homologous protein (CHOP), which is one of the key effectors of the endoplasmic reticulum stress response (60).

**Local Anesthetics Promote Cancer Cell Death**

Many preclinical studies suggested the capacity of LAs to induce apoptosis after triggering the activation of tumor suppressor protein p53 (TP53) (61), DNA damage (62), dissipation of the mitochondrial transmembrane potential (48, 51, 63, 64), ROS production (51, 64, 65) or activation of the mitogen-activated protein kinase (MAPK) pathway (64). LAs can provoke mitochondrial rupture and cause the release of pro-apoptotic molecules such as cytochrome c (48, 63, 64) and SMAC (61). In addition, LAs upregulate the pro-apoptotic proteins Bax, Bak (31, 34, 42, 43, 47, 55, 64, 66) and down-regulate their antagonist BCL-2 (34, 42, 63, 64, 66). This ultimately favors the formation of the apoptosome (composed by APAF1, caspase 9 and cytochrome c) (67) and the proteolytic activation of a range of pro-caspases (30, 34, 51, 61–64, 68) including pro-caspase 3 (31, 34, 42, 47, 48, 51, 63, 64, 66, 69–71) and in fine the cleavage of poly (ADP-ribose) polymerase 1, marking the apoptotic death of cancer cells (31, 51, 63, 64, 66, 67, 71).

**LOCAL ANESTHETICS MAY POSSESS INDIRECT ANTITUMORAL EFFECTS BY SUSTAINING THE IMMUNE SYSTEM**

Surgery per se induces stress responses involving endocrine and metabolic reactions which generate acute inflammation and interact with the immune system (6). From incision, afferent nerve pathways stimulate catecholamine production and activate the corticotropic axis (6). The increase of plasma cortisol and catecholamine levels modifies the distribution of circulating leukocytes leading to lymphopenia and promotes the synthesis of the pro-tumoral cytokine IL-6, hence potentially enhancing tumor progression. Epinephrine and norepinephrine may act on beta-adrenergic receptors found in several tumor types such as breast, prostate or liver cancer and stimulate cancer cell proliferation and migration (72, 73). The adrenocorticotropic hormone (ACTH) interferes with antibody synthesis and inhibits the production of interferon (IFN) by T cells (74). This glucocorticoid stress is sufficient to profoundly subvert anticancer immunosurveillance in a range of murine models (4). In this context, it appears important to note that regional anesthesia by LAs injected into the epidural space provides a stable pain relief by blocking nociceptive pathways. Moreover, different neuroaxial anesthetic modalities possess the outstanding capacity to minimize glucocorticoid stress during surgery and to counteract the immunodepression induced by general anesthesia. Assessment of cortisol, epinephrine and norepinephrine in the serum and in the urine of patients after laparotomy under spinal anesthesia were significantly decreased during peri- and postoperative period compared to patients under general anesthesia (75–78). Thus, LAs could prevent the neuroendocrine stress responses resulting from oncological surgery and sustain anticancer immunity. This is strongly suggested by a preclinical study of Bar-Yosef et al., in which spinal block using bupivacaine not only controlled pain in rats during laparotomy but also attenuated the post-surgical dissemination of metastases (79) Figure 2.

Acute pain generated by surgery also compromises NK cell-mediated immunity, which is in the first line of defense against tumor development (80, 81), and fosters T helper lymphocyte polarization towards a Th2 profile (82). These findings highlight the need for optimal perioperative analgesia and the necessity to strengthen the immune system. Of note, at clinically relevant concentrations lidocaine enhances the cytotoxic effect of NK cells assessed by the release of lytic granules (granzyme B and perforin) (83). In addition, the serum from patients receiving LAs during tumor resection (independently of the route of administration) was particularly competent to kill cancer cells (84, 85), to preserve lymphocyte proliferation and to attenuate apoptosis of peripheral blood lymphocytes. The ratio of Th1/Th2 cells inclined towards a Th1 profile with secretion of IFN-γ (86). Finally, the level of Th17 and regulatory T cells (Tregs) was also significantly lower compared to the control group (87) Table 1 and Figure 2.

Another hypothesis that might explain indirect anticancer effects of LAs is their capacity to blunt surgical inflammatory effects. Despite the employment of minimally surgical procedures, the production of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and the inhibition of IFN-γ responses occur from the incision of the patient’s skin (82). Inflammation is marked by major vascular and exudative phenomena (edema, diapedesis and congestion) compromising the endothelial barrier and thus facilitating the formation of new metastases. Secretion of inflammatory cytokines also stimulates MMP-9 and VEGF production in the tumor-surrounding tissue and activates Src kinase that compromises vessel barrier integrity and facilitates cancer cell migration through the extracellular matrix (94). Moreover, the cytokine IL-6 produced in the microenvironment exerts a pro-tumor activity (95). IL-6 directly stimulates the proliferation and survival of cancer cells by stimulating the advancement of the cell cycle, the expression of anti-apoptotic molecules and angiogenesis (72, 96). In addition, IL-6 exerts immunosuppressive effects by inhibiting dendritic cells and lymphocytes, by activating Tregs and in fine by promoting tumor immune escape. In clinical practice, high levels of IL-6 predict chemotherapy resistance and poor prognosis in many type of cancers (97). Taken together, these data suggest that the anti-inflammatory effects of LAs may contribute to sustain immune effectors and to reduce tumor progression. Indeed, several randomized controlled trials showed a significant decrease of IL-1, IL-6, IL-8 and MMP-3 and-9 in the serum of patients after LA injection (88, 89, 92). Unfortunately, the impact on clinical outcomes has not yet been investigated Table 1 and Figure 2.

**LOCAL ANESTHETICS COULD IMPACT ON ONCOLOGICAL OUTCOMES**

Local Anesthetics Potentiate Conventional Anticancer Treatments

Primary tumor resection is often combined with neo-adjuvant or adjuvant anticancer treatments (chemotherapy, radiotherapy or immunotherapy) shortly before or after the surgical procedure.
Interestingly, LAs can sensitize cancer cells to conventional antitumor therapeutics. Thus, the cytotoxic effects of chemotherapy (with 5-fluorouracil, paclitaxel, cisplatin or carboplatin) or protein kinase inhibitors (such as vemurafenib or erlotinib) were significantly potentiated by LAs (25, 27, 50, 54, 58, 68, 98, 99). Associated with 5-aza-2′-deoxycytidine, lidocaine showed additive demethylating effects in breast cancer cells (57). In vivo, the combination of cisplatin and LAs increased life span and cure rate in several mouse models (42, 100, 101), contrasting with the observation that bosutinib reversed the anti-metastatic effect of lidocaine (38). Surprisingly, procaine demonstrated an unexpected protection against cisplatin-induced nephrotoxicity as indicated by reduced blood urea nitrogen and renal tubular degeneration (102).

Local Anesthetics Improve Overall Survival After Cancer Surgery

Many retrospective clinical studies investigated the impact of LAs on oncological prognosis. Thirteen trials suggest a potential benefit of LA injection on recurrence free survival and overall survival after cancer surgery compared to control groups. For instance, in a cohort of 588 patients undergoing primary colon cancer resection, epidural anesthesia improved the five-year survival after adjustment for relevant patient characteristics,
which may affect immunosurveillance as well as the combination with other anesthetics (opioids, volatile agents), the drug used for local anesthesia and its posology, various independent factors such as cancer type, comorbidities, effects of LAs are different. After gastro-esophageal resection, epidural analgesia appeared as an independent predictor of longer recurrence-free survival \([\text{HR} = 0.74, 95\% \text{ CI } 0.56-0.95, p=0.036]\) (104). In the study of Cummings et al. involving 42 151 patients, the use of neuroaxial anesthesia significantly improved overall survival \([\text{HR} = 0.91, 95\% \text{ CI } 0.87-0.94, p<0.001]\) (103). After hepatic resection for colorectal metastases, epidural analgesia appeared as an independent predictor of longer recurrence-free survival \([\text{HR} = 0.74, 95\% \text{ CI } 0.56-0.95, p=0.036]\) (104). After gastro-esophageal resection, epidural analgesia increased the time to recurrence \([\text{HR} = 0.33, 95\% \text{ CI } 0.17-0.63, p<0.0001]\), and overall survival \([\text{HR} = 0.42, 95\% \text{ CI } 0.21-0.83, p<0.0001]\) at 2 years of follow-up (105). It should be noted that ten retrospective trials failed to confirm these findings. However, the putative anticancer effects of LAs are difficult to demonstrate as they are influenced by various independent factors such as cancer type, comorbidities, the drug used for local anesthesia and its posology (concentration, exposure time, administration route), as well as the combination with other anesthetics (opioids, volatile agents), which may affect immunosurveillance as well Table 2.

Irrespective of these limitations, four large meta-analyses all concluded in favor of beneficial effects of epidural anesthesia alone or associated with general anesthesia. With 14 studies including 47 000 patients, Chen et al. demonstrated an improved overall survival of epidural anesthesia compared with general anesthesia \([\text{HR} = 0.84, 95\% \text{ CI } 0.74-0.96, p=0.013]\) (15). In the meta-analysis by Pei et al., combined general-epidural anesthesia was associated with decreased recurrence and metastasis rate in the subgroup of prostate cancer patients and in the subgroup with follow-up less than or equal to 2 years \((OR = 0.66, 95\% \text{ CI } 0.51-0.98, p=0.035; \text{respectively})\) (16). Sun et al. showed similar results with a significant better overall survival for patients receiving perioperative regional anesthesia \([\text{HR} = 0.84, 95\% \text{ CI } 0.75-0.94; F^2 =41\%]\) compared to the control group (17). Finally, the meta-analysis by Weng et al. involving 21 studies and 51 620 patients concluded that neuroaxial anesthesia improved both overall survival \([\text{HR} = 0.853, \text{CI}=0.741-0.981, p=0.026]\) and recurrence-free survival \([\text{HR} = 0.846, \text{CI}=0.718-0.998, p=0.047]\) (18) Table 3.

### Table 1: Trials assessing local anesthetics on biological markers.

| Cancer | Patients | Design | Biological markers outcome |
|--------|----------|--------|---------------------------|
| Breast N=17 | Control group: general anesthesia (sevoflurane) + opioid | PVB decreased IL-1β, MMP-3, MMP-9 and increased IL-10 |
| Breast N=15 | Studied group: general anesthesia (propofol) + PVB (bupivacaine) | |
| Breast N=20 | Studied group: general anesthesia (propofol) + PVB (bupivacaine) + fentanyl | |
| Breast N=20 | Control group: general anesthesia (sevoflurane) | PVB decreased IL-6, increased IL-12, IFN-γ and IL-10/IFN-γ ratio |
| Breast N=15 | Control group: general anesthesia (sevoflurane) | No significant difference in VEGF and PGE2 values between groups |
| Breast N=20 | Control group: general anesthesia (sevoflurane) | Increased VEGF after surgery in the general anesthesia group |
| Breast N=20 | Control group: general anesthesia (bupivacaine) bolus and infusion for 48h | |
| Cervical N=15 | Control group: general anesthesia (sevoflurane) + fentanyl | Epidural analgesia decreased the requirement of morphine and stress response (blood glucose and serum cortisol) |
| Cervical N=15 | Studied group: general anesthesia (sevoflurane) + fentanyl + bolus and infusion of lidocaine | |
| Colon N=20 | Control group: general anesthesia (desflurane) + epidural (ropivacaine + morphine) | Epidural analgesia decreased the requirement of morphine and stress response (blood glucose and serum cortisol) |
| Colon N=20 | Studied group: general anesthesia + epidural analgesia (lidocaine bolus and infusion) + Postoperative epidural (ropivacaine + morphine) | |
| Colon N=20 | Studied group: general anesthesia + epidural analgesia (lidocaine bolus and infusion) + epidural (ropivacaine + morphine) | |
| ENT N=15 | Control group: general anesthesia (sevoflurane) + morphine | Epidural analgesia decreased the requirement of morphine and stress response (blood glucose and serum cortisol) |
| ENT N=15 | Studied group: general anesthesia (sevoflurane) + epidural (ropivacaine) | |
| Liver N=30 | Control group: general anesthesia (sevoflurane) Postoperative: morphine | Epidural shifted Th1/Th2 balance (Th1 dominance) and decreased Th17 and Treg cells |
| Liver N=31 | Studied group: general anesthesia (sevoflurane) + epidural (ropivacaine); Postoperative: bupivacaine + morphine | |
| Ovary N=30 | Control group: general anesthesia (propofol) + fentanyl | Epidural group: higher NK cell cytotoxicity, higher serum concentrations of IL-10 and IFN-γ and lower serum concentrations of IL-1β and IL-8 |
| Ovary N=31 | Studied group: general anesthesia (propofol) + fentanyl + epidural (ropivacaine + lidocaine bolus and infusion) | |
| Ovary N=20 | Control group: general anesthesia (volatile agents) + intraperitoneal ropivacaine | Intrapерitoneal ropivacaine reduced time of chemotherapy initiation |

**ENT**, ear nose throat; **IL**, interleukin; **IV**, intravenous; **MMP**, metalloproteinase; **NK**, natural killer; **PCA**, patient-controlled analgesia; **PGE2**, prostaglandin E2; **PVB**, paravertebral block; **TGF**, tumor growth factor; **VEGF**, vascular endothelial growth factor.
**TABLE 2** | Retrospective studies assessing local anesthetics impact on cancer prognosis.

| Cancer          | Patients | Design                                                                 | Cancer prognosis outcome                                                                 | Ref |
|-----------------|----------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-----|
| Breast          | N=79     | Control group: general anesthesia (sevoflurane) Postoperative: PCA (morphine) | Studied group: lower recurrence-and metastasis-free survival (p=0.012)                        | (14) |
|                 | N=50     | Studied group: general anesthesia (sevoflurane) + PVB (bolus and infusion of levobupivacaine for 48h) |                                                                              |     |
| Cervical        | N=69     | Control group: general anesthesia                                         | Studied group: not associated with lower cancer burden or a reduced risk of tumor recurrence and mortality | (106) |
|                 | N=63     | Studied group: neuraxial anaesthesia (spinal and epidural analgesia)       |                                                                              |     |
| Colon           | N=2,299  | Control group: general anesthesia + opioid-based analgesia                | No association between epidural analgesia and recurrence or death                   | (107) |
|                 | N=449    | Studied group: loading dose of lidocaine + general anesthesia and epidural anesthesia (bupivacaine with or without fentanyl for 48-72h) |                                                                              |     |
| Colon           | N=668    | Control group: general anesthesia                                          | Peridural analgesia: not associated with better oncological outcome                 | (108) |
|                 | N=208    | Studied group: epidural anesthesia                                         |                                                                              |     |
| Colon           | N=189    | Control group: general anesthesia                                         | Epidual analgesia: better 5-year survival (p=0.01)                                      | (8)  |
|                 | N=399    | Studied group: general anesthesia                                          |                                                                              |     |
| Colon           | N=253    | Control group: general anesthesia                                          | Epidual: lower cancer recurrence in patients older than 64 years                     | (109) |
|                 | N=256    | Studied group: epidural anesthesia                                         |                                                                              |     |
| Colon           | N=32,481 | Control group: general anesthesia                                          | Epidual analgesia: improved survival (p<0.001)                                          | (103) |
|                 | N=9,670  | Studied group: epidural analgesia                                          |                                                                              |     |
| Colo-rectal     | N=93     | Control group: general anesthesia sevoflurane or desflurane + fentanyl and IV morphine for 2 to 5 days | Epidual analgesia: lower mortality in the sub-group of rectal cancer (p=0.049)          | (110) |
|                 | N=562    | Studied group: general anesthesia sevoflurane or desflurane + epidural (bolus local anesthetic and fentanyl) or local anesthetic alone and infusion of local anesthetic with fentanyl or local anesthetic and morphine for 2-5 days |                                                                              |     |
| Colo-rectal     | N=173    | Control group: general anesthesia sevoflurane or desflurane + fentanyl and IV morphine for 48h | No significant difference in overall survival or disease-free survival at 5 years       | (111) |
|                 | N=107    | Studied group: epidural anesthesia (Bolus and infusion of bupivacaine with fentanyl for 48h) |                                                                              |     |
| Colo-rectal     | N=307    | Control group: general anesthesia (isoflurane or desflurane + fentanyl)   | Epidual analgesia: greater long-term survival (p<0.02)                                   | (9)  |
|                 | N=442    | Studied group: general anesthesia (isoflurane or desflurane + fentanyl) + epidural analgesia |                                                                              |     |
| Colo-rectal +   | N=120    | Control group: IV anesthesia                                               | Epidual analgesia: improved five-year recurrence free survival (p=0.036)               | (104) |
| Liver metastases |         | Studied group: epidural analgesia                                          |                                                                              |     |
| Gastro-         | N=140    | Control group: general anesthesia (sevoflurane or propofol infusion) + IV opioid analgesia | Epidual was associated with 2-year recurrence and overall survival benefit (p<0.0001) | (105) |
| oesophageal     | (total)  | Studied group: general anesthesia (sevoflurane or propofol) + epidural anesthesia (bupivacaine bolus + infusion with morphine for 96h) |                                                                              |     |
| ENT             | N=160    | Control group: general anesthesia + morphine                               | Epidual analgesia increased cancer-free survival (p=0.04) and overall survival (p=0.03) | (112) |
|                 | N=111    | Studied group: general anesthesia + epidural analgesia                    |                                                                              |     |
| Liver           | N=244    | Control group: general anesthesia (sevoflurane or propofol) + sufentanil + nonsteroidal anti-inflammatory drugs | Local anesthetic increased recurrence free survival (p=0.002) and overall survival (p=0.036) | (12)  |
| Melanoma        | N=221    | Control group: general anesthesia (southone or propofol) + sufentanil or remifentanil | Spinal anesthesia: a trend of better cumulative survival rate                          | (113) |
|                 | N=82     | Studied group: spinal anesthesia (bupivacaine)                            | No difference on recurrence-free survival or overall survival                        |     |
| NSCLC           | NA       | Control group: general anesthesia (isoflurane, sevoflurane or desflurane) + IV opioid analgesia; postoperative PCA (hydroromorphine, fentanyl or morphine) |                                                                              |     |
|                 |          | Studied group: general anesthesia (isoflurane, sevoflurane or desflurane) + IV opioid analgesia |                                                                              |     |
|                 |          | Postoperative: epidural (bupivacaine + fentanyl or bupivacaine + hydromorphone or ropivacaine and fentanyl) |                                                                              |     |
| Ovary           | N=37     | Control group: general anesthesia (sevoflurane or isoflurane) + PCA fentanyl | Epidual analgesia: greater 3- and 5-year overall survival rates (p=0.043)              | (10)  |
|                 | N=106    | Studied group: epidural anesthesia (Infusion of bupivacaine or ropivacaine and morphine for 48h) |                                                                              |     |
| Ovary           | N=43     | Control group: general anesthesia (volatile + fentanyl)                   | Epidual analgesia: not associated with improved overall survival or time to recurrence | (115) |
|                 |          | Postoperative: ketorolac and PCA (morphine)                              |                                                                              |     |
| Pancreas        | N=2,239  | Control group: general anesthesia (sevoflurane) + epidural analgesia (ropivacaine) | L工业园acine group: longer overall survival (p=0.013)                                 | (11)  |
| (total)         |          | Studied group:lidocaine bolus+ continuous infusion + general anesthesia (sevoflurane) + epidural analgesia (ropivacaine); |                                                                              |     |

* (Continued)
Finally, among 11 prospective randomized controlled trials, two studies reported a better disease-free survival after epidural anesthesia (ropivacaine or bupivacaine) associated with intravenous or volatile agents during colon (p=0.012) or bladder tumor resection (p=0.02) compared to general anesthesia alone (119, 120). One study investigated the antitumor activity of patient sera after levobupivacaine infiltration during breast cancer resection. A significant blockade of MDA-MB-231 breast carcinoma cells was observed (p=0.01) (121). A better survival after hepatectomy was also noticed after infiltration of ropivacaine close to the incision site (p=0.029) (122). However, other trials failed to confirm these findings, perhaps due to a lack of power and major confusion bias compromising data analyses (injection of multiple different anesthetic agents, inclusion of cancers at different stages, loss of patients due to deficient followup, heterogenous groups...). Table 4 Multicenter randomized controlled trials with high quality methodology are urgently awaited to definitely conclude on the potential benefit of LAs on oncological outcomes.

Until now, no guidelines and no recommendations in onco-anesthesia are available to guide clinical practice. Indeed, most of the results issued from clinical studies are not convincing enough to elaborate new guidelines due to a lack of power, presence of bias, heterogeneity of groups and the combined use of various anesthetics that exert conflicting effects on tumor cells. However, based on the sheer number of prospective multicenter randomized controlled trials, we may expect the translation of preclinical data into the clinics for the near future. Thus, we anticipate that Phase III clinical trials will confirm that, beyond their useful analgesic properties, local anesthetics exert antitumor effects, meaning that their use will be approved for this additional indication.

### DISCUSSION

Oncological surgery generates neuroendocrine stress, inflammation and acute pain responsible for immunosuppression, hence impacting on the antitumor immune response (4, 83). The manipulation of the tumor by the surgeon, vascular invasion and the peri-operative synthesis of VEGF also promote the migration and proliferation of residual cancer cells and thus, future metastatic recurrence (131).

The impact of local anesthetics on cancer and its recurrence after surgery has spurred a wave of interest over the last decade. Two recent reviews covering this field have been published (132, 133).

| Cancer | Patients | Design | Cancer prognosis outcome | Ref |
|--------|----------|--------|--------------------------|-----|
| Prostate | N=123 | Control group: general anesthesia (propofol) + fentanyl | Epidural anesthesia: lower risk of recurrence (p=0.012) | (13) |
|         | N=102 | Postoperative: PCA (morphine) | | |
| Prostate | N=158 | Control group: general anesthesia (isoflurane) + fentanyl; Postoperative: ketorolac + paracetamol | Epidural analgesia: improved clinical progression-free survival (p=0.002) | (116) |
|         | N=103 | Studied group: general anesthesia (isoflurane) + Epidural (bupivacaine) + fentanyl | | |
| Prostate | N=533 | Control group: intravenous analgesia | | |
|         | N=578 | Studied group: epidural analgesia | | |
| Visceral | N=63 | Control group: general anesthesia (isoflurane + fentanyl); Postoperative: morphine | | |
|         | N=69 | Epidural group: bupivacaine + general anesthesia (isoflurane); postoperative: bupivacaine + morphine | | |

### TABLE 3 | Meta-analyses assessing local anesthetics impact on cancer prognosis.

| Cancer | Patients | Design | Cancer prognosis outcome | Ref |
|--------|----------|--------|--------------------------|-----|
| Solid tumors | 14 studies (47,000 patients) | Control group: general anesthesia | Epidural anesthesia improved overall survival (p=0.013). | (15) |
|         | Studied group: epidural anesthesia with or without general anesthesia | | | |
| Solid tumors | 10 studies (3,254 patients) | Control group: combined general-epidural anesthesia | Combined general-epidural anesthesia was associated with decreased recurrence (p=0.027) and metastasis rate (p=0.035) within the subgroup of prostate cancer patients and the subgroup with follow-up less than or equal to 2 years | (16) |
|         | Studied group: perioperative regional anesthesia | | | |
| Solid tumors | 20 studies (NA) | Control group: general anesthesia | Perioperative regional anesthesia associated with improved overall survival [HR] = 0.84, 95% CI, 0.75-0.94; I² =41% | (17) |
|         | Studied group: perioperative regional anesthesia | | | |
| Solid tumors | 21 studies (51,620 patients) | Control group: general anesthesia | Neuroaxial anesthesia improved overall survival (p=0.026) and recurrence-free survival (p=0.047) | (18) |
|         | Studied group: neuroaxial anesthesia combined with or without general anesthesia | | | |

IV, intravenous; PCA, patient-controlled analgesia; PVB, paravertebral block.
PCA, patient-controlled analgesia; IV, intravenous.

### TABLE 2 | Continued

| Cancer | Patients | Design | Cancer prognosis outcome | Ref |
|--------|----------|--------|--------------------------|-----|
| Prostate | N=102 | Studied group: general anesthesia (propofol) + fentanyl | Epidural analgesia: improved clinical progression-free survival (p=0.002) | (117) |
|         | | Postoperative: local anesthetic infusion for 48-72h | | |
| Prostate | N=158 | Control group: general anesthesia (isoflurane) + fentanyl; Postoperative: ketorolac + paracetamol | Epidural analgesia: not associated with a significant effect | (117) |
|         | N=103 | Studied group: general anesthesia (isoflurane) + Epidural (bupivacaine) + fentanyl | | |
| Prostate | N=533 | Control group: intravenous analgesia | A trend in favor of epidural anesthesia was observed for recurrence free survival | (118) |
|         | N=578 | Studied group: epidural analgesia | | |
| Visceral | N=63 | Control group: general anesthesia (isoflurane + fentanyl); Postoperative: morphine | | |
|         | N=69 | Epidural group: bupivacaine + general anesthesia (isoflurane); postoperative: bupivacaine + morphine | | |

Wu Chuang et al. Local Anesthetics Induce Cancer Cell Death
Preclinical studies found that LAs have direct molecular effects on mitochondrial metabolism, indirectly improve cancer immunosurveillance. In addition, LAs showed a remarkable ability to decrease cancer cell death (39). These direct antitumor effects described in many clinical studies noticed that LAs used for extradural block attenuated the immunosuppressive endocrine effects generated by surgery (75). In addition, an array of retrospective trials and meta-analyses concluded that LAs used alone or in combination with general anesthesia preserved NK cell activity and improved overall survival and recurrence-free survival (18).

In the present article we attempted to synthesize the current preclinical and clinical state of the art, while evoking the capacity of local anesthetics to stimulate anticancer immune responses, thereby potentiating the efficacy conventional anticancer therapies. Particular emphasis has been laid on the difference direct effects impacting on cancer cells and indirect, immune-mediated effects controlling residual tumor cells that mediate local relapse or distant metastasis.

LAs possess analgesic and anti-inflammatory properties that indirectly improve cancer immunosurveillance. In addition, LAs have direct molecular effects on mitochondrial metabolism, generate oxidative stress, trigger apoptosis pathways in cancer cells and activate NK cells (34, 64). Preclinical studies found that treatment of cancer cells with clinically relevant concentrations of LAs inhibits their proliferation and migration or induces cell death (39). These direct antitumor effects described in many cancer cell lines are time- and concentration-dependent. In murine models, LAs showed a remarkable ability to decrease the incidence of metastases after surgery (35, 38). In humans, several clinical studies noticed that LAs used for extradural block

| Cancer | Patients | Design | Cancer prognosis outcome |
|--------|----------|--------|--------------------------|
| Bladder | N=150 | Control group: general anesthesia (sevoflurane)+fentanyl | Local anesthesia: longer disease-free survival (p=0.02) |
| | N=510 | Studied group (propofol)+lidocaine+ epidural (ropivacaine) | (119) |
| Breast | N=11 | Control group: local incision analgesia (ropivacaine bolus + infiltration) | Postoperative (morphine) | Patient serum from studied group reduced MDA-MB-231 breast carcinoma cell proliferation (p=0.01) |
| | N=30 | Control group: general anesthesia (volatile anesthetic) + PVB (bupivacaine bolus + infusion) | (121) |
| | N=30 | Studied group: general anesthesia (volatile anesthetic) + PVB (bupivacaine bolus and infusion) | No difference between groups |
| | N=1066 | Control group: general anesthesia (sevoflurane) | (123) |
| | N=1043 | Control group: general anesthesia (propofol) + PVB | No difference between groups |
| | N=68 | Control group: general anesthesia (propofol) | (124) |
| | N=66 | Studied group: general anesthesia + single injection PVB (ropivacaine) | No difference between groups |
| | N=59 | Studied group: general anesthesia + continuous-PVB (ropivacaine for 72h) | (125) |
| Colon | N=85 |Control group: general anesthesia (isoflurane)+ fentanyl | Epidural improved survival in patients without metastases (p=0.012) |
| | N=30 |Control group: general anesthesia (isoflurane)+ fentanyl + epidural group (bupivacaine) | (120) |
| Rectum | N=30 |Control group: general anesthesia (propofol+ remifentanil); postoperative: PCA fentanyl | No difference for postoperative NK cell cytotoxicity and IL-2, recurrence or metastasis |
| Liver | N=20 |Control group: tramadol injections | Ropivacaine increased postoperative survival (p=0.029) |
| | N=20 |Control group: local incision analgesia (ropivacaine bolus + infiltration) | (122) |
| Lung | N=200 |Control group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanil); postoperative: PCA morphine | No difference between groups for recurrence-free and overall survival |
| | N=200 |Studied group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanil)+ epidural anesthesia (ropivacaine) | (127) |
| Prostate | N=50 |Control group: general anesthesia; postoperative: morphine | No difference between groups |
| | N=49 |Studied group: general anesthesia + ropivacaine bolus and infusion with fentanyl | (128) |
| Solid | N=216 |Control group: general anesthesia; postoperative: opioid-based analgesia | No difference between groups |
| Tumors | N=230 |Control group: general anesthesia + epidural group (bupivacaine or ropivacaine); postoperative: continuous bupivacaine or ropivacaine + fentanyl or pethidine | (129) |
| Solid | N=822 |Control group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanil/ fentanyl); postoperative: PCA morphine | No difference between groups for overall survival |
| Tumors | N=772 |Control group: general anesthesia (propofol/sevoflurane+ sufentanyl/remifentanil/ fentanyl)+ epidural anesthesia (ropivacaine) | (130) |

PCA, patient-controlled analgesia; NK, natural killer; PVB, paravertebral block.
randomized multicenter prospective trials dealing with the potential anticancer effects of LAs are urgently awaited. Indeed, the confirmation that LAs improve patient outcome would have a major impact on clinical practice, in particular in the context of oncological surgery.

**AUTHOR CONTRIBUTIONS**

AW provided the list of trials and designed the figures. OK helped for the design of figures. GK and LB wrote the manuscript. All authors contributed to the article and approved the submitted version.

**FUNDING**

OK is supported by Institut National du Cancer (INCa) and the DIM Elicit of the Ile-de-France; LB received a research grant by Bristol Myers Squibb Foundation France. AW was supported by El Programa Nacional de Becas “Don Carlos Antonio Lopez” (BECAL). GK is supported by the Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; AMMIca US23/CNRS UMS3655; Association pour la recherche sur le cancer (ARC); Association “Ruban Rose”; Cancéropôle Ile-de-France; Fondation pour la Recherche Médicale (FRM); a donation by Elior; Equipex Onco-Pheno-Screen; European Joint Programme on Rare Diseases (EJPDR); Gustave Roussy Odysséea, the European Union Horizon 2020 Projects Oncobiome and Crimson; Fondation Carrefour; INCa; Inserm (HTE); Institut Universitaire de France; LabEx Immuno-Oncology (ANR-18-IDEX-0001); the Leducq Foundation; a Cancer Research ASPIRE Award from the Mark Foundation; the RHU Turin Lumière; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and Personalized Medicine (CARPEM). This study contributes to the IdEx Université de Paris ANR-18-IDEX-0001.

**REFERENCES**

1. Ferlay J, Lam F, Colombet M, Mery L, Pineros M, et al. Global Cancer Observatory: Cancer Today (2020). Lyon: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today (Accessed February 2021).

2. Sullivan R, Alatise OL, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global Cancer Surgery: Delivering Safe, Affordable, and Timely Cancer Surgery. *Lancet Oncol* (2015) 16(11):1193–224. doi: 10.1016/S1470-2045(15)00223-5

3. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging Biological Principles of Metastasis. *Cell* (2017) 168(4):670–91. doi: 10.1016/j.cell.2016.11.037

4. Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, et al. Stress-Glucocorticoid-TSC22D3 Axis Compromises Therapy-Induced Antitumor Immunity. *Nat Med* (2019) 25(9):1428–41. doi: 10.1038/s41591-019-0566-4

5. Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, et al. Increased Surgical Stress Promotes Tumor Metastasis. *Surgery* (2003) 133(5):547–55. doi: 10.1067/msy.2003.141

6. Salmon P, Kaufman L. Preoperative Anxiety and Endocrine Response to Surgery. *Lancet* (1990) 335(8701):1340. doi: 10.1016/0140-6736(90)92155-V

7. Ramirez MF, Ai D, Bauer M, Vauthey JN, Gottumukkala V, Kee S, et al. Innate Immune Function After Breast, Lung, and Colorectal Cancer Surgery. *J Surg Res* (2015) 194(1):185–93. doi: 10.1016/j.jss.2014.10.030

8. Vogelaar FJ, Abegg R, van der Linden JC, Corneliis HG, van Dorsten FR, Lennems VE, et al. Epidural Analgesia Associated With Better Survival in Colon Cancer. *Int J Colorectal Dis* (2015) 30(8):1103–7. doi: 10.1007/s00384-015-2224-8

9. Holler JP, Ahlbrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, et al. Periural Analgesia may Affect Long-Term Survival in Patients With Colorectal Cancer After Surgery (PACO-RAS-Study): An Analysis of a Cancer Registry. *Ann Surg* (2013) 258(6):899–93. doi: 10.1097/SLA.0b013e3182915861

10. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic Technique may Affect Prognosis for Ovarian Serous Adenocarcinoma: A Retrospective Analysis. *Br J Anaesthesia* (2011) 106(6):814–22. doi: 10.1093/bja/aer055

11. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, et al. Association Between Intraoperative Intravenous Lidocaine Infusion and Survival in Patients Undergoing Pancreatectomy for Pancreatic Cancer: A Retrospective Study. *Br J Anaesthesia* (2020) 125(2):141–8. doi: 10.1016/j.bja.2020.03.034
Local Anesthetics Induce Cancer Cell Death

Wu Chuang et al.

24. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, et al. (2012) 12:11145–55. doi: 10.1477/CMA.2012.097495

25. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, et al. Local Anesthetics Inhibit Kinesin Motility and Microtubule Proliferations in Human Epithelial and Breast Tumor Cells. Breast Cancer Res Treat (2011) 129(3):691–701. doi: 10.1007/s10549-010-1239-7

26. Zhang Y, Peng X, Zheng Q, Ropivacaine Inhibits the Migration of Esophageal Cancer Cells via Sodium-Channel-Independent But Premylanly-Dependent Inhibition of Rac1/JNK/PAK/FAK. Biochem Biophys Res Commun (2018) 501(4):1074–9. doi: 10.1016/j.bbrc.2018.05.110

27. Zheng Q, Peng X, Zhang Y. Cytotoxicity of Amide-Linked Local Anesthetics on Melanoma Cells via Inhibition of Ras and RhoA Signaling Independent of Sodium Channel Blockade. BMC Anesthesiol (2020) 20(1):43. doi: 10.1186/s12871-020-00957-4

28. Li C, Gao S, Li X, Li C, Ma L. Proacaine Inhibits the Proliferation and Migration of Colon Cancer Cells Through Inactivation of the ERK/FAK Pathways by Regulation of RhoA. Oncol Res (2018) 26(2):209–17. doi: 10.3727/096504017X14944568573622

29. Zhang N, Xing X, Gu F, Zhou G, Liu X, Li B. Ropivacaine Inhibits the Growth, Migration and Invasion of Gastric Cancer Through Attenuation of WEE1 and PI3K/AKT Signaling via mIIR-520a-3p. Oncotargets Ther (2020) 13:3509–21. doi: 10.2147/OTT.S244550

30. Sun H, Sun Y. Lidocaine Inhibits Proliferation and Metastasis of Lung Cancer Via Regulation of miR-539-EGFR Axis. Artif Cells Nanomed Biotechnol (2019) 47(1):2866–74. doi: 10.1080/21691401.2019.1636807

31. Ying B, Huang H, Li H, Song M, Wu S, Ying H. Proacaine Inhibits Proliferation and Migration and Promotes Cell Apoptosis in Osteosarcoma Cells by Upregulation of MicroRNA-133b. Oncol Res (2017) 25(9):1463–70. doi: 10.3726/096504017X1487851291077

32. Piegeler T, Schlapfer M, Dull RO, Schwartz DE, Borget A, Minshall RD, et al. Clinically Relevant Concentrations of Lidocaine and Ropivacaine Inhibit TNFα-Induced Inhibition of Lung Adenocarcinoma Cells In Vitro by Blocking the Activation of Akt and Focal Adhesion Kinase. Br J Anaesthesia (2015) 115(5):784–91. doi: 10.1093/bja/aev341

33. Qin A, Liu Q, Wang J. Ropivacaine Inhibits Proliferation, Invasion, Migration and Promotes Apoptosis of Papillary Thyroid Cancer Cells Via Regulating ITGA2 Expression. Drug Dev Res (2020) 81(6):700–7. doi: 10.1002/ddr.22167

34. Wada H, Seki S, Takahashi T, Karasawa-Nishi N, Higuchi H, Habu Y, et al. The Antioxidant N-Acetyl Cysteine Suppresses Lidocaine-Intracellular Reactive Oxygen Species Production and Cell Death in Neuronal SH-SY5Y Cells. BMC Anesthesiol (2016) 16(1):104. doi: 10.1186/s12871-016-0273-3

35. Link P, Berger R, Hollmann MW, Feigl H. Lidocaine Time- and Dose-Dependently Dimethylates Deoxyribonucleic Acid in Breast Cancer Cell Lines In Vitro. Br J Anaesthesia (2012) 109(2):200–7. doi: 10.1093/bja/aes128

36. Villar-Garea A, Fraga MF, Espada J, Esteller M, Proacaine is a DNA-Demethylating Agent With Growth-Inhibitory Effects in Human Cancer Cells. Cancer Res (2003) 63(16):4984–9.

37. Sabit H, Samy MB, Said OA, El-Zawahri MM. Procaine Induces Epigenetic Changes in HCT116 Colon Cancer Cells. Genet Res (2016) 2016:8348450. doi: 10.1155/2016/8348450

38. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of Perioperative Lidocaine on Metastasis After Sevoflurane or Flurane or Propofol and Propofol on Pulmonary Metastasis in a Murine Model of Breast Cancer Surgery. Cancers (2019) 11(5):1–12. doi: 10.3390/cancers11050613

39. Wall TP, Crowley PD, Sherwin A, Foley AG, Bugay DJ. Effects of Lidocaine and SrC Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. Cancers (2019) 11(10):1–10. doi: 10.3390/cancers11101414

40. Chen J, Jiao Z, Wang A, Zhong W. Lidocaine Inhibits Melanoma Cell Proliferation by Regulating ERK Phosphorylation. J Cell Biochem (2019) 120(4):6402–8. doi: 10.1002/jcb.27927

41. Tada M, Imazeki F, Fukai K, Sakamoto A, Arai M, Mikata R, et al. Procaine Inhibits the Proliferation and DNA Methylation in Human Hepatoma Cells. Hepatol Int (2007) 1(3):355–64. doi: 10.1007/s12285-006-0014-5

42. Sabatí M, Ibarz M, Roca C, Pardelló R, Alcañiz M, Tordera J, et al. Redox Mechanism of Levobupivacaine Cytostatic Effect on Human Tongue Cancer Cells With Inhibition of the Activity of Epidermal Growth Factor Receptor. Anesthesiology Analesis (2006) 102(4):1103–7. doi: 10.1213/01.ane.0000198330.84341.35

43. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, et al. Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells In Vitro and in a Xenograft Model In Vivo. Anesthesiology (2017) 126(5):868–81. doi: 10.1097/ALN.0000000000001528

44. Ye L, Zhang Y, Chen YJ, Liu Q. Anti-Tumor Effects of Lidocaine on Human Gastric Cancer Cells In Vitro. Brasiliatines Lekarske Listy (2019) 120(3):212–7. doi: 10.4149/BLL_2019_036

45. Le Gac G, Angenard G, Clement B, Laviolle B, Coulouan C, Beloel H. Local Anesthetics Inhibit the Growth of Human Hepatocellular Carcinoma Cells. Anesth Analg (2017) 125(5):1600–9. doi: 10.1213/ANE.0000000000002429

46. Jose C, Hebert-Chatelain E, Dias Amoedo N, Benediti E, Ippoliti R, et al. Local Anesthetics Counteract Cell Proliferation and Migration of Human Triple-Negative Breast Cancer and Melanoma Cells. J Cell Physiol (2020) 245(1):2347–48. doi: 10.1002/jcp.28926

47. Gao Z, Xu Z, Huang MS, Lin YC, Wang T, Gao M, et al. Procaine and Proacainamide Inhibit the Wnt Canonical Pathway by Promoting Wnt-CaM Signalling. Br J Anaesthesia (2018) 120:150–6. doi: 10.1093/bja/aes128

48. Villar-Garea A, Fraga MF, Espada J, Esteller M, Proacaine is a DNA-Demethylating Agent With Growth-Inhibitory Effects in Human Cancer Cells. Cancer Res (2003) 63(16):4984–9.
59. Xia W, Wang L, Yu D, Ma X, Zhou X. Lidocaine Inhibits the Progression of Retinoblastoma In Vitro and In Vivo by Modulating the Mir203a3p/EGFR Axis. Mol Med Rep (2019) 20(2):1333-42. https://doi.org/10.3892/mmr.2019.10363

60. Li T, Chen L, Zhao H, Wu L, Masters J, Han C, et al. Both Bupivacaine and Levobupivacaine Induce Colon Cancer Cell Growth But Not Melanoma Cells In Vitro. J Anesthesia (2019) 33(1):17-25. doi: 10.1007/s00540-018-2577-6

61. Tat T, Juri A, Selicena C, Pasca S, Ionescu D. Antiproliferative Effects of Propofol and Lidocaine on the Colon Adenocarcinoma Microenvironment. J BUON Off J Balkan Union Oncol (2019) 24(1):106–15.

62. Chang YC, Hsu YC, Liu CL, Huang SY, Hu MC, Cheng SP. Local Anesthetics Induce Apoptosis in Human Breast Tumor Cells. Analgesia Anesthesiology (2014) 118(1):116–24. doi: 10.1213/ANE.0b013e3182a49479

63. Chang YC, Hsu YC, Liu CL, Huang SY, Hu MC, Cheng SP. Local Anesthetics Induce Apoptosis in Human Thyroid Cancer Cells Through the Mitogen-Activated Protein Kinase Pathway. PloS One (2014) 9(2): e89563. doi: 10.1371/journal.pone.0089563

64. Wang HW, Wang LY, Jiang L, Tian SM, Zhong TD, Fang XM. Amide-Linked Local Anesthetics Induce Apoptosis in Human Non-Small Cell Lung Cancer. J Thorac Dis (2016) 8(10):2748–57. doi: 10.21037/jtd.2016.09.66

65. Lu J, Xu SY, Zhang QG, Xu R, Lei HY. Bupivacaine Induces Apoptosis via Mitochondria and P38 MAPK Dependent Pathways. Eur J Pharmacol (2011) 657(1-3):51-8. doi: 10.1016/j.ejphar.2011.01.055

66. Mirabehn S, Shielde TG, de Neocochea-Campion R, Yuan X, Januza A, Williams NL, et al. Bupivacaine and Lidocaine Induce Apoptosis in Osteosarcoma Tumor Cells. Clin Orthopaedics Related Res (2021) 479(1):180-94. https://doi.org/10.1007/CO/R000000000001510

67. Zhang X, Zhu M, Xu Z, Li W, Dong X, Chen Y, et al. Ropivacaine Promotes Tumor Growth and Metastasis by Promoting Expression of the Mitogen-Activated Protein Kinase Pathway. Mol Cancer (2021) 20(1):36. doi: 10.1186/s12943-021-01202-9

68. Zhang X, Pang W, Liu H, Wang J. Bupivacaine Induced Ovarian and Prostate Cancer Apoptotic Cell Death. J Cell Biochem (2013) 124(1):180-97. doi: 10.1002/jcb.20785

69. Liang Y, Ji J, Lin Y, He Y, Liu J. The Ganglioside GM-1 Inhibits Bupivacaine-Induced Neurotoxicity in Mouse Neuroblastoma Neuro2a Cells. Cell Biochem Funct (2016) 34(6):455-62. doi: 10.1002/cbf.3208

70. Xuan W, Zhao H, Hankin J, Chen L, Yao S, Ma D. Local Anesthetic Bupivacaine Induced Ovarian and Prostate Cancer Apoptotic Cell Death and Underlying Mechanisms In Vitro. Sci Rep (2016) 6:26277. doi: 10.1038/srep26277

71. Zhang H, Lin J, Hu T, Ren Z, Wang W, He Q. Effect of miR-132 on Bupivacaine-Induced Neurotoxicity in Human Neuroblastoma Cell Line. J Pharmacol Sci (2019) 139(3):186-92. doi: 10.1515/jpharmsci-2019-01314

72. Bernabe DG, Tamae AC, Basilio ER, Oliveira SH. Stress Hormones Increase Cell Proliferation and Regulates Interleukin-6 Secretion in Human Ovarian Squamous Cell Carcinoma Cells. Brain Behav Immun (2011) 25(3):574-83. doi: 10.1016/j.bbi.2010.12.012

73. Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JL, et al. Norepinephrine Uregulates VEGF, IL-8, and IL-6 Expression in Human Melanoma Tumor Cell Lines: Implications for Stress-Related Enhancement of Tumor Progression. Brain Behav Immun (2009) 23(2):267–75. doi: 10.1016/j.bbi.2008.10.005

74. Baker GH, Irani MS, Byrom NA, Nagyekar NM, Wood RJ, Hobbs JR, et al. Stress, Cortisol Concentrations, and Lymphocyte Subpopulations. Br Med J (1985) 290(6479):1393. doi: 10.1136/bmj.290.6479.1393

75. Carli F, Webster J, Pearson M, Pearson J, Bartlett S, Bannister P, et al. Protein Concentrations of Lidocaine on Natural Killer Cell Cytotoxicity. Anesthet Analg Pain Med (2020) 24(1):106. doi: 10.1016/j.pain.2019.01.014

76. O’Brian SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC, Inhibition of the Stress Response to Breast Cancer Surgery by Regional Anesthesia and Analgesia Does not Affect Vascular Endothelial Growth Factor and Prostaglandin E2. Anesthesia Analgesia (2005) 100(1):244–9. doi: 10.1213/00000542-20041336.37946.7D

77. Looney M, Doran P, Buggy DJ. Effect of Anesthetic Technique on Serum Vascular Endothelial Growth Factor C and Transforming Growth Factor Beta in Women Undergoing Anesthesia and Surgery for Breast Cancer. Anesthesiology (2010) 113(5):1118–25. doi: 10.1097/ALN.0b013e318179a69

78. Kochhar A, Banday J, Ahmad Z, Panjpar P, Vajifdar H. Cervical Epideral Analgesia Combined With General Anesthesia for Head and Neck Cancer Surgery: A Randomized Study. J Anaesth Clin Pharmacol (2020) 36(2):182–6. doi: 10.4103/jocp.JOCAP_72_19

79. Bar-Yosef S, Melamed R, Page GG, Shahrar G, Shahrar K, Ben-Eliyahu S. Attenuation of the Tumor-Promoting Effect of Surgery by Spinal Blockade in Rats. Analgesiology (2001) 94(6):1066–73. doi: 10.1007/978-0-07-900452-4-00106000-00022

80. Sacerdote P, Manfredi B, Bianchi M, Panerai AE. Interim But Not Continuous Inescapable Footshock Stress Affects Immune Responses and Immunocyte Beta-Endorphin Concentrations in the Rat. Brain Behav Immun (1994) 8(3):251–60. doi: 10.1016/bb.1994.1023

81. Ben-Eliyahu S, Page GG, Yirmiya R, Shahrar G. Evidence That Stress and Surgical Interventions Promote Tumor Development by Suppressing Natural Killer Cell Activity. Int J Cancer (1999) 80(6):880–8. doi: 10.1002/(SICI)1097-0215(19990315)80:6<880::AID-IJC1433;1.0.CO;2-Y

82. Lin E, Calvano SE, Lowry SF. Inflammatory Cytokines and Cell Response in Surgery. Surgery (2000) 127(2):117–26. doi: 10.1016/mss.2010.1584

83. Ramirez MF, Tran P, Kata JP. The Effect of Clinically Therapeutic Plasma Concentrations of Lidocaine on Natural Killer Cell Cytotoxicity. Regional Anesthesia Pain Med (2015) 40(1):3-8. doi: 10.1097/AAP.00000000000000191

84. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DJ, Mascha E, et al. Anesthetic Technique and the Cytokine and Matrix Metalloproteinase Response to Primary Breast Cancer Surgery. Regional Anesthesia Pain Med (2010) 35(6):490–5. doi: 10.1097/AAP.0b013e3181f79a69

85. Sultan SS. Paravertebral Block can Attenuate Cytokine Response When it Replaces General Anesthesia for Cancer Breast Surgeries. J Anesthesia Pain Med (2011) 24(1):182–9. doi: 10.3892/apm.2011.5052

86. Wang HL, Yan HD, Liu Y, Sun BZ, Huang R, Wang XS, et al. Intraoperative Intraveneous Lidocaine Exerts a Protective Effect on Cell-Mediated Immunity in Patients Undergoing Radical Hysterectomy. Mol Med Rep (2015) 12(5):7039–44. doi: 10.3892/mmr.2015.4235

87. Zhou D, Gu FM, Gao Q, Li QL, Zhou J, Miao CH. Effects of Anesthetic Methods on Preserving Anti-Tumor T-Helper Polarization Following Hepatectomy. World J Gastroenterol (2012) 18(24):3088–98. doi: 10.3748/wjg.v18.i24.3089

88. Whelan P, Morris PJ. Immunological Responsiveness After Transurethral Resection of the Prostate: General Versus Spinal Anesthetic. Clin Exp Immunol (1982) 48(3):611–8.
Maccio A, Maddeddu C. Inflammation and Ovarian Cancer. Cytokine (2012) 58(2):133–47. doi: 10.1016/j.cyto.2012.01.015

Wu Y, Yang J, Guo Y, Yu Y, Bao I, Niu W, et al. Regulatory Effect of E2, IL-6 and IL-8 on the Growth of Epithelial Ovarian Cancer Cells. Cell Mol Immunol (2005) 2(5):365–72.

Browning L, Patel MR, Horvath EB, Tawara K, Jorcyk CL. IL-6 and Ovarian Cancer: Inflammatory Cytokines in Promotion of Metastasis. Cancer Manage (2018) 10:668–93. doi: 10.2147/CMAJ.S179189

Li K, Yang J, Han X. Lidoicane Sensitizes the Cytotoxicity of Cisplatin in Breast Cancer Cells via Up-Regulation of RARbeta2 and RASSFLA Demethylation. J Mol Med (2014) 12(1):2519–36. doi: 3.390/jmmj151233519

Zhu G, Zhang L, Dan J, Zhu Q. Differential Effects and Mechanisms of Local Anesthetics on Esophageal Carcinoma Cell Migration, Growth, Survival and Chemosensitivity. BMC Anesth (2020) 20(1):126. doi: 10.1186/s12871-020-01039-1

Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, et al. Effect of Perioperative Lidocaine and Cisplatin on Metastasis in a Murine Model of Breast Cancer Surgery. Anticancer Res (2018) 38(10):5999–606. doi: 10.21873/anticanceres.12894

Viale M, Vannozzi MO, Mandyv V, Esposito M. Time-Dependent Influence of Procarine Hydrochloride on Cisplatin Antitumor Activity in P388 Tumor Bearing Mice. Anticancer Res (2001) 21(1A):485–7.

Esposito M, Fulco RA, Collecchi P, Zanca A, Cadoni A, Merlo F, et al. Improved Therapeutic Index of Cisplatin by Procarine Hydrochloride. J Natl Cancer Inst (1990) 82(8):677–84. doi: 10.1093/jnci/82.8.677

Cummings KC 3rd. Xu F, Cummings LC, Cooper GS. A Comparison of Epidural Analgesia and Traditional Pain Management Effects on Survival and Cancer Recurrence After Colorectomy: A Population-Based Study. Anesthesiology (2012) 116(4):797–806. doi: 10.1097/ALN.0b013e318246746f

Zimmitti G, Soliz J, Aioia TA, Gottomukkala V, Cat JP, Tseng CW, et al. Positive Impact of Epidural Analgesia on Oncologic Outcomes in Patients Undergoing Resection of Colorectal Liver Metastases. Ann Surg Oncol (2016) 23(3):1003–11. doi: 10.1245/s10434-015-4933-1

Hiller JG, Hacking MB, Link EK, Wessels KL, Riedel BJ. Perioperative Epidural Analgesia Reduces Cancer Recurrence After Gastro-Oesophageal Surgery. Acta Anaesthesiologica Scandinavica (2014) 58(3):281–90. doi: 10.1111/aan.12255

Ismail H, Ho KM, Narayan K, Kondalsamy-Chennakesavan S. Effect of Neuraxial Anaesthesia on Tumour Progression in Cervical Cancer Patients Treated With Brachytherapy: A Retrospective Cohort Study. Br J Anaesthesia (2010) 105(2):145–9. doi: 10.1093/bja/aep156

Wu HL, Tai YH, Mandell MS, Tsou MY, Yang SH, Chen TH, et al. Effect of Epidural Analgesia on Cancer Prognosis After Colon Cancer Resection: A Single-Centre Cohort Study in Taiwan. BMJ Open (2020) 10(1):e036577. doi: 10.1136/bmjopen-2019-036577

Wurster EF, Planka F, Warschowk R, Antony P, Brenner T, Weigand MA, et al. Peridural Analgesia Does Not Impact Survival in Patients After Colon Cancer Resection: A Retrospective Propensity-Adjusted Analysis. Int J Colorectal Dis (2019) 34(7):1283–93. doi: 10.1007/s00384-019-03315-0

Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, et al. Association Between Epidural Analgesia and Cancer Recurrence After Colorectal Cancer Surgery. Anesthesiology (2010) 113(1):27–34. doi: 10.1097/ALN.0b013e3181d6bd8d

Gottschalk A, Brodner G, Van Aken HK, Ellger B, Althaus S, Schulze HJ, Can Regional Anaesthesia for Lymph-Node Dissection Improve the Prognosis in Malignant Melanoma? Br J Anaesthesia (2012) 109(2):253–9. doi: 10.1093/bja/aes176

Critt DR, Zimmitti G, Nourissat A, Molliex S, Zufferey PJ. Cervical Anaesthesia on Tumour Progression in Cervical Cancer Patients Undergoing Resection of Colorectal Liver Metastases. Br J Anaesthesia (2012) 116(4):797–806. doi: 10.1097/BMA.0b013e318246746f

Bintz M, Tournay E, Billard V, Rey A, Cay J. Major Abdominal Surgery for Cancer: Does Epidural Analgesia Have a Long-Term Effect on Recurrence-Free and Overall Survival? Annales Francaises D’anesthesie Reanimation (2013) 32(5):e81–8. doi: 10.1016/j.jframer.2013.02.027

Guerreiro Orellach JL, Raigón Ponerverted A, Malo Manso A, Herrera Imbroda B, Escalona Belmonte JJ, Ramirez Allega M, et al. Anaesthesia in Combination With Propofol Increases Disease-Free Survival in Bladder Cancer Patients Who Undergo Radical Tumour Cystectomy as Compared to Inhalational Anaesthetics and Opiate-Based Anaesthetics. Oncology (2020) 98(3):161–7. doi: 10.1159/000504087

Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-Term Survival After Colon Cancer Surgery: A Variation Associated With choice of Anaesthesia. Anesth Analg (2008) 107(1):325–32. doi: 10.1213/anesthesia-2008-00516

Deegan CA, Murray D, Doran P, Ercimovic P, Moriarty DC, Buggy DJ, Effect of Anaesthetic Technique on Oestrogen Receptor-Negative Breast Cancer Cell Function In Vitro. Br J Anaesthesia (2009) 103(5):685–90. doi: 10.1093/bja/aep261

Wu YF, Li YP, Wu YB, Chen L, Jiang CB, Li DY, et al. Postoperative Local Anaesthesia for Acute Pain Treatment in Patients With Hepatocellular Carcinoma. Rev Da Associacao Med Brasileira (2018) 64(1):175–80. doi: 10.1590/1806-9282.64.02.175

Finn DM, Ilfeld BM, Untart JT, Madison SJ, Suresh PJ, Sandhu NPS, et al. Post-Mastectomy Cancer Recurrence With and Without a Continuous Peripheral Block in the Immediate Postoperative Period: A Prospective Multi-Year Follow-Up Pilot Study of a Randomized, Triple-Blinded, Placebo-Controlled Investigation. J Anaesthesia (2017) 31(3):374–9. doi: 10.1007/s00540-017-2345-5

Sessler DI, Pei L, Huang Y, Fleischman E, Marhofer P, Kanzur A, et al. Recurrence of Breast Cancer After Regional or General Anaesthesia: A Randomised Controlled Trial. Lancet (2019) 394(10121):1807–15. doi: 10.1016/S0140-6736(19)32313-X

Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, et al. Survival Analysis of Patients With Breast Cancer Undergoing A Modified Radical Mastectomy With or Without a Thoracic Paravertebral Block: A 5-Year Follow-Up of a Randomized Controlled Trial. Anticancer Res (2017) 37(10):5813–20

Kim SY, Kim NK, Baik SH, Min BS, Hur H, Lee J, et al. Effects of Postoperative Pain Management on Immune Function After Laparoscopic Resection of Colorectal Cancer: A Randomized Controlled Study. Medicine (2016) 95(3):e3602. doi: 10.1097/MD.0000000000003602

Zou ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, et al. Epidural Anaesthesia-Andes of Local Anesthesia and Cancer Recurrence After Radial Prostatectomy. Can J Anaesthesia J Canadien D’anaesthesie (2010) 57(2):107–12. doi: 10.1136/s12630-009-9214-7
Conflict of Interest: OK is scientific co-founder of Samsara Therapeutics; GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytx Pharma, PharmaMar, Samsara, Sanofi, Vascage and Vasculox/Tioma. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Samsara Therapeutics and Therafast Bio. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.