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Trial watch: local anesthetics in cancer therapy

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ABSTRACT

Preclinical evidence indicates potent antitumor properties of local anesthetics. Numerous underlying mechanisms explaining such anticancer effects have been identified, suggesting direct cytotoxic as well as indirect immunemediated effects that together reduce the proliferative, invasive and migratory potential of malignant cells. Although some retrospective and correlative studies support these findings, prospective randomized controlled trials have not yet fully confirmed the antineoplastic activity of local anesthetics, likely due to the intricate methodology required for mitigating confounding factors. This trial watch aims at compiling all published preclinical and clinical research, along with completed and ongoing trials, that explore the potential antitumor effects of local anesthetics.

Introduction

Several retrospective clinical trials noted a significantly improved overall survival (OS) in cancer patients following the administration of local anesthetics (LAs) during the perioperative period and the surgical removal of primary tumors.[1–3] This observation prompted extensive preclinical studies aiming to investigate the underlying molecular mechanisms, altogether leading to the initiation of prospective clinical trials. The objective of this review is to provide an overview of crucial findings from both fundamental and clinical research, including ongoing prospective trials in this domain. In the first part of this work, we focus on preclinical studies investigating the intrinsic antitumor properties of LAs *in vitro* and *in vivo*. In the second part, we comprehensively summarized published clinical trials studying the potential impact of LAs employed during cancer surgery on postoperative outcome. Finally, we discuss ongoing clinical trials and hypothetical future updates in oncoanesthesia.

1. Preclinical investigation

1.1. Local anesthetics: anti-migrative and anti-mitotic effects

1.1.1. Anti-migrative property

Certain anesthetics that are currently employed in clinical practice for their analgesic properties have been shown to improve disease outcome in cancer patients following local application during oncosurgery. In line with this, LAs including lidocaine, tetracaine, and procaine were found to inhibit the adherence, migration and proliferation of various types of cancer cells *in vitro*.[4–8] Local as well as systemic injections of lidocaine (at concentrations used in

surgery) minimized the occurrence of pulmonary metastases in mouse osteosarcoma[9] and breast cancer models *in vivo*.[10–12] Some of these effects might be explained by the fact that LAs act on voltage-gated sodium and calcium channels (thus blocking pain conduction in neurons) which are also highly expressed in invasive tumors.[13] By inhibiting calcium channels, LAs impinge on intracellular Ca^{2+} levels, which can affect (among other things) actin polymerization and induce cytoskeletal rearrangements.[14] Moreover, LAs have the capacity to modulate the expression of vimentin and E-cadherin, which are both involved in cell adhesion *via* the formation of dynamic microtubule protrusions and tubulin microtentacles, respectively.[15] Furthermore, the LA-mediated modulation of intracellular Ca^{2+}, limits the shedding of heparin-binding epidermal growth factor-like growth factor (HB-EGF), which is a key driver of invasiveness and metastasis in many human cancers.[9] Altogether, LAs can limit the aggregation and attachment of malignant cells.[16]

Furthermore, lidocaine was shown to inhibit the CXCL12-CXCR4 axis and to block transient receptor potential melastatin 7 (TRPM7) in human glioma and breast cancer cells, resulting in proliferative arrest and the inhibition of cell migration.[17–19] Lidocaine was also found to inhibit the WNT/beta-catenin pathway, thus blocking epithelial-mesenchymal transition and impairing the progression of ovarian cancer.[20] Bupivacaine reportedly interferes with gastric cell migration by blocking the RHO-A/RHO-associated protein kinase (ROCK)/myosin light chain (MLC) pathway, and ropivacaine reduces the migration of esophageal and thyroid cancer cells by inhibiting the RAS-related C3 botulinum toxin substrate 1/c-JUN N-terminal kinase/paxillin/focal adhesion kinase (RAC1/JNK/paxillin/FAK) pathway and integrin-alpha-2 expression,

respectively.[21–23] Moreover, ropivacaine may interact with integrin-beta1, which is involved in tumorigenesis, ultimately inducing apoptosis.[24] Additionally, LAs may impact on matrix metalloproteinases (MMPs), retarding the dissemination of tumor cells through the extracellular space and thus decreasing the invasion of distant organs.[11,23,25,26]

Collectively, these findings indicate that LAs can impair malignant cell migration, block epithelial-mesenchymal transition and reduce the metastatic potential through different mechanisms, including the inhibition of cytoskeletal remodeling, the inhibition of HB-EGF shedding and a limitation of MMP activity.

1.1.2. Anti-mitotic property

LAs also exhibit short-term cytostatic and long-term cytotoxic properties.[27] Interestingly, the chemical structure (ester or amide) does not seem to dictate cytotoxicity activity, whereas it is worth noting that chloroprocaine and prilocaine, which possess a short duration of action, induce fewer effects on cancer cells than agents with an extended time of efficacy.[28] Among the tested LAs, bupivacaine appears to be the most cytotoxic, while procaine is the least.

A number of mechanisms have been described for the cytostatic and cytotoxic effects induced by LAs. Thus lidocaine was shown to inhibit epidermal growth factor receptor (EGFR) activity[29,30] and to upregulate cytoplasmic polyadenylation element-binding protein 3 (CPEB3) in hepatocellular carcinoma.[31] Moreover, lidocaine exerts anti-proliferative effects in bladder cancer cells by inhibiting isoprenylcysteine carboxylmethyltransferase, which coordinates posttranslational prenylation, thus affecting RAS and RHO-A-dependent signaling pathways.[32,33] Both lidocaine and ropivacaine also halt the proliferation of melanoma and gastric cancer cells by inhibiting extracellular signal-regulated kinases 1/2 (ERK1/2).[34,35] Certain LAs have may promote DNA damage and modulate the Phosphatidylinositol-3-kinase/Protein kinase B/mammalian target of rapamycin complex (PI3K/AKT/mTORC) axis, thus inhibiting cyclins and cyclin-dependent kinases (CDK) and inducing cell cycle arrest (or delay) at either the G0/1-S phase or at the S/G2/M transition.[7,23,26,34,36–47] Enduring cytostatic stress can lead to the activation of apoptotic cell death pathways such as the p38 mitogen-activated protein kinase (MAPK) pathway, which results in the oligomerization of pro-apoptotic BAX and BAK, mitochondrial membrane permeabilization, the subsequent release of cytochrome c (CYTC) along with the formation of the apoptosome and the activation of effector caspases, resulting in the cleavage of substrates including poly ADP-ribose polymerase (PARP), in both solid tumors and hematopoietic malignancies.[5,23,36,39,41,42,48–65] Further to the induction of apoptosis some articles also suggested that LAs may promote additional cell death modalities such as necrosis and ferroptosis.[46,66–71]

Of note, LAs can trigger the release of danger-associated molecular patterns (DAMPs) linked to immunogenic cell death (ICD), such as ATP and high mobility group box 1 (HMGB1), yet fail to promote the exposure of calreticulin at the plasma membrane.[28,72] ICD is accompanied by pre-mortem cellular stress responses, namely autophagy and endoplasmic reticulum (ER) stress that often precede and trigger the activation of various modalities of cell death. At clinically relevant concentrations, bupivacaine, chloroprocaine, levobupivacaine, lidocaine, ropivacaine and prilocaine induce the formation of autophagosomes, as indicated by the lipidation of autophagy-related protein light-chain 3B (LC3B), and activate the three arms of ER stress: i) the protein kinase RNA-like endoplasmic reticulum kinase (PERK) catalyzing the phosphorylation of eukaryotic initiation factor 2 alpha (EIF2A), which then favors the translation of activating transcription factor 4 (ATF4); ii) the inositol-requiring enzyme 1 (IRE1), which leads to the alternative splicing of X-box binding protein 1 (XBP1) mRNA; and iii) the cleavage of activating transcription factor 6 (ATF6) in the Golgi apparatus. Once activated, these transcription factors (ATF4, ATF6, XBP1) translocate into the nucleus where they turn on the expression of pro-apoptotic genes such as the C/EBP homologous protein (CHOP).[28,61,63–65,73]

1.2. Epigenetic effect

LAs can induce epigenetic changes that impact cell migration and viability. At clinically relevant concentrations, LAs reduce global methylation in cancer cells by inhibiting DNA methyltransferases (DNMTs), which in turn leads to the demethylation of CpG islands, thus restoring activity at epigenetically silenced loci including the expression of tumor suppressor genes.[40,53,74–77] Procaine has been shown to enhance the expression of Wnt inhibitory factor-1 (WIF-1) gene, which is silenced due to promoter hypermethylation in lung cancers.[78] Furthermore, lidocaine decreases the expression of EGFR by up-regulating miR-520a-3p and miR-539, thus inhibiting proliferation and promoting apoptosis in colorectal, retinoblastoma and lung cancer cells.[51,79,80] Lidocaine, ropivacaine and bupivacaine inactivate cellular signaling including the MEK-ERK, PI3K/AKT/MTORC and nuclear factor-kappa B (NF-kB) pathways, by up-regulating miR-145 and miR-520a-3p, thus attenuating malignant growth and inhibiting migration in different model of cancer.[15,81–84] Lidocaine and bupivacaine can downregulate DANCR long noncoding RNA (lncRNA) by the induction of miR-187-5p and then suppress the proliferation of MCF-7 breast cancer cells.[85] Similarly in cervical cancer cells, lidocaine inhibits proliferation and promotes apoptosis through the increased expression of the lncRNA of maternally expressed gene 3 (MEG3).[86] Lidocaine also interferes with the regulation of circular RNA (circRNA), microRNA (miRNA) and messenger RNA (mRNA) species affecting cellular development and progression at all levels.[87–91] Ropivacaine induces cell cycle arrest in cervical cancer cells by inhibiting miR-96-mediated the maternally expressed gene 2/signal transducer and activator of transcription 3 (MEG2/pSTAT3) signaling,[92] triggers apoptosis in glioma cells by impacting on the miR-424-5p/SNHG16 axis,[93] retards invasion and migration of choriocarcinoma by modulating the opioid growth factor receptor pseudogene 1 (OGFRP1) lncRNA and the miR-4731-5p/hypoxia-inducible factor 3A (HIF3A) axis,[94] suppresses the proliferation of glioblastoma via an impact on the miR-21-5p/lysine acetyltransferase 8 (KAT8) axis[95] and represses the progression of breast cancer by regulating miR-27b-3p/Yes-

associated protein 1 (YAP).[96] Moreover, lidocaine upregulates microRNA-493 and miR-30c and thus sensitizes melanoma and cutaneous carcinoma to 5-fluorouracil and cisplatin, respectively.[97,98] Moreover, down-regulation of miR-21 and miR-10b by lidocaine reportedly overcomes cisplatin resistance in lung cancer cells.[99,100]

In summary, these findings suggest that LAs exhibit potent epigenetic anticancer effects by reactivating epigenetically silenced genes and by modulating the expression of a set of miRNAs, lncRNAs and circRNAs, altogether impacting malignant progression.

1.3. Immune effects

LAs exert a broad impact on various immune effectors including the activity and proliferation of lymphocytes and natural killer (NK) cells. *In vitro*, in ovarian and pancreatic cancer as well as in lymphoblastic and acute leukemia cells, lidocaine increases the expression of NKG2D receptor, thus stimulating the cytolytic activity of NK cells.[101,102] Furthermore, in the randomized controlled trial reported by Wei *et al.*, 62 patients with breast tumor resection were randomly assigned to intravenous lidocaine treatment or placebo. In this trial, a significant decrease in $CD3^+$, $CD4^+$ T cells and $CD4^+/CD8^+$ ratio was noticed in the control group, but lidocaine stabilized the level of immune effectors during postoperative period. Moreover, in patients treated with lidocaine the number of circulating NK cells decreased less rapidly in the postoperative period than in the control group.[103] In the study of Yardeni *et al.* 65 women undergoing hysterectomy were allocated to receive either intravenous lidocaine or placebo. Serum analysis revealed higher proliferation of lymphocytes and lower serum level of IL-6 in lidocaine treated patients as compared to the placebo group.[104] Similarly, Wang *et al.* observed that infusion of lidocaine during cancer uterine surgery preserves the balance Th1/Th2, improves the secretion of the antitumor IFN-γ, and attenuates apoptotic demise of lymphocytes.[105] Epidural injection of LAs also increased the serum concentration of IFN-γ, enhanced NK cell cytotoxicity, preserves Th1/Th2 ratio, and decreased pro-inflammatory cytokines such as IL1-β and IL-8, suggesting that the immune effects of LAs do not depend on the mode of administration but rather on their intrinsic properties.[106,107]

Simultaneously, LAs reduce the function of immunosuppressive effectors such as regulatory T cells (Tregs) and T helper 17 cells (Th17) *in vitro*.[28,102,105–107] Moreover, lidocaine and ropivacaine possess the ability to induce the maturation of dendritic cells into antigen-presenting cells while stimulating phagocytosis, thus facilitating tumor antigen presentation and allowing for the onset of antitumor responses and the development of immune memory. Furthermore, when injected intratumorally, LAs induce abscopal effects in tumors established in immunocompetent mice and sensitize cancers to immunotherapy with immune checkpoint inhibitors.[28,108] In essence, LAs play a crucial role in modulating the tumor microenvironment, rendering tumors more responsive to immunotherapy.[109,110]

1.4. Metabolic effects

1.4.1. Mitochondrial dysfunction

LAs have been shown to mediate time – and dose-dependent effects on mitochondrial fusion and to induce dysfunction in energy-intensive cells such as cardiomyocytes, neurons, and cancer cells.[28] Following LA treatment, all complexes of the respiratory chain are inhibited, disrupting the primary source of energy production by halting oxidative phosphorylation. Additionally, the levels of two glycolytic enzymes, glucose 1,6-bisphosphate, and fructose 1,6-bisphosphate, are decreased. Mitochondrial disturbance is further manifested by the breakdown of the mitochondrial transmembrane potential and the production of reactive oxygen species.[28,41,43,48,49,52,60,111,112] As a result, mitochondrial dysfunction leads to the release of pro-apoptotic molecules, such as cytochrome *c*, triggering caspase activation and inducing the cell death of malignant cells.[41,49,60]

1.4.2. Neuroendocrine effect

Surgical procedures induce both local and systemic inflammatory pain, activating the corticotropic axis. The released cortisol and catecholamines negatively impact various immune effectors involved in immunosurveillance and the antitumor immune response. This results in suppressed leukocyte chemotaxis, impairment of the lytic activity of NK cells and T lymphocytes, decreased synthesis of immunoglobulins by plasma cells, and inhibition of the release of cytolytic interferon-γ (IFN-γ).[113] Pro-inflammatory and pro-tumor cytokines such as IL-6, IL-10, and TNF-α are also generated, stimulating the production of MMP-9 and vascular endothelium growth factor (VEGF), thus contributing to carcinogenesis and angiogenesis.[114–117]

Due to their substantial anti-inflammatory and analgesic properties, LAs effectively mitigate surgical pain and glucocorticoid stress, thus supporting the immune system.[118,119] In a rat model of surgical pain, the addition of spinal block to general anesthesia significantly reduced surgery-induced lung metastases.[113] Furthermore, through their anti-inflammatory properties, lidocaine, ropivacaine, and chloroprocaine impede Src protein tyrosine kinase (Src)-dependent inflammatory signaling, reducing MMP-9 secretion and phosphorylation of cell-cell adhesion molecule-1. This contributes to the anti-invasiveness and metastatic effects.[25,120]

1.4.3. Metabolite modulation

Lidocaine induces changes in intracellular metabolite levels by downregulating several pathways related to glutaminolysis, as well as choline, phosphocholine and total choline syntheses. This impact on the metabolomic profile contributes to the antiproliferative and anti-invasive activities of LAs.[121]

1.5. Synergistic effects

Surprisingly, several preclinical studies have observed remarkable synergistic effects when conventional anticancer therapies such as anthracyclines, taxanes, or platinum salts were combined with LAs, resulting in significantly potentiated antitumor activity *in vitro* and prolonged survival of cancer bearing mice *in vivo*.[6,21,33,42,76,111,122–128] Combination of LAs with

chemotherapy or immunotherapy, such as anti-programmed cell death protein 1 (PD-1) antibodies, significantly decreases tumor growth and improves OS in various mouse models of fibrosarcoma, breast tumors, and colon adenocarcinoma.[28,129–132] Thus, lidocaine enhanced the cytotoxicity of the CDK 4/6 inhibitor palbociclib in triple-negative breast cancer cells.[133] Lidocaine also sensitized human breast cancer cells to cisplatin induced cell death and potentiated its metastasis-inhibiting action.[124,125] Interestingly, in some cases, the combination of LAs with anticancer-therapy was shown to mitigate side effects, such as cisplatin-induced nephrotoxicity, thus offering the possibility of enhancing the chemotherapy dose.[126] In sum, each of the aforementioned local anesthetics can interfere with properties acquired by malignant cells, thus impeding their ability to survive, resist to cell death, proliferate, evade growth suppressors, induce angiogenesis, alter the immune system, promote inflammation and genome instability, deregulate cellular energetics or activate local invasion (Figure 1).
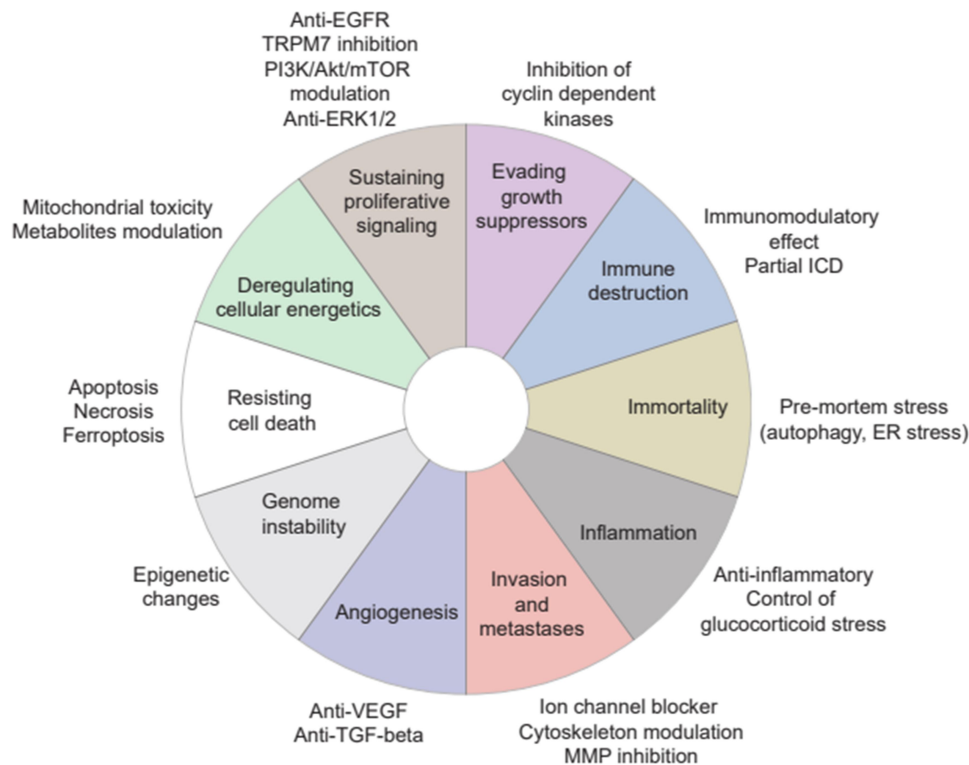
2. Clinical investigation

2.1. Retrospective studies and meta-analyses

Among 51 retrospective observational trials, 24 studies reported beneficial effect following the administration of LA during the removal of primary solid tumors. Importantly, positive outcome was not influenced by the mode of administration and occurred both with injections close to the tumor site (regional block, local injection, infusion through a catheter) and at a distance (spinal anesthesia, epidural, intravenous injection).[1–3,134–145] For instance, intravenous lidocaine administered during cystectomy, ovariectomy or pancreatectomy increased OS and disease-free survival (DFS), emerging as an independent factor for better prognosis.[136,146,147] Local injection of lidocaine during hepatectomy decreased the incidence of recurrence and the rate of death.[137] Levobupivacaine, administered through paravertebral block to optimally control pain after mastectomy, was associated with increased recurrence-free survival (RFS) in breast cancer patients.[2] Epidural administration of LAs during the peri – and postoperative period of major surgical procedures was linked to better OS and DFS, lower recurrence rates and reduced postoperative complications such as pneumonia and anastomotic leakage. No LA appeared to be superior to another[1,3,134,135,138–144,148–154] (Table 1).

However, two articles concluded that LAs injected *in epidural* could be predictors of worse RFS and might increase mortality after cystectomy or hepatectomy.[155,156] Finally, 25 trials observed no association between LAs and outcome.[157–181] These results were combined in four meta-analyses, the conclusions of which confirmed the benefit of LAs injected through neuro-axial procedures during the perioperative period (Table 2). This benefit includes a decrease in the incidence of relapses and an improvement in both OS and DFS.[182–185]

Figure 1. Anti-tumor properties of local anesthetics according to the hallmarks of cancer determined by Hanahan and Weinberg. Cancer cells acquire distinct hallmarks that allow them to survive, resist to cell death mechanisms and possess immortality, evade growth suppressors, proliferate, induce angiogenesis, alter the immune system, promote an inflammatory environment, create genome instability, deregulate cellular energetics, and activate invasion and migration processes. Each anti-tumor property of local anesthetics can target one of these acquired hallmarks of cancer cells and hence interfere with the oncogenesis process. *EGFR, epithelial growth factor receptor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; ICD, immunogenic cell death; MMP, matrix metalloproteinase; PI3K/Akt/mTOR, Phosphatidylinositol-3-kinase/Protein kinase B/mammalian target of rapamycin; TGF-β, transforming growth factor β; TRPM7, transient receptor potential melastatin 7; VEGF, vascular endothelial growth factor.*

Table 1. Retrospective studies investigating the oncological impact of local anesthetics.

Tumor surgery	Local anesthetic	Design	Results	Ref.
Abdominal	Bupivacaine (epidural)	One hundred and thirty-two patients included (69 with epidural)	No association with RFS	157
Bladder	LA (epidural)	Four hundred and thirty-nine patients involved (215 with epidural).	Do not decrease risk of recurrence ($p = .05$). Epidural was a predictor of worse RFS ($p = .009$) and cancer-specific survival ($p = .03$)	155
Bladder	Lidocaine (intravenous)	One hundred and forty-four patients included.	Higher survival ($p = .009$). Less recurrence ($p = .0023$). Independent good prognosis factor (HR = 0.36, 95%CI [0.15–0.90]; $p = .029$).	146
Bladder	LA (epidural)	One thousand six hundred and twenty-eight patients included (887 epidural)	No benefit in improved short-term outcomes, cancer-specific survival ($p = .804$) or OS ($p = .136$)	158
Breast	Levobupivacaine (paravertebral)	One hundred and twenty-nine patients included (50 with paravertebral block)	Association between paravertebral block and RFS ($p = .012$)	2
Breast	LA (paravertebral)	Seven hundred ninety-two women involved (188 paravertebral)	No benefit in RFS ($p = .172$)	159
Cervix	LA (neuraxial)	One hundred and thirty-two patients treated with brachytherapy under neuraxial (n = 63) or GA (n = 69).	No benefit in recurrence ($p = .863$), in long-term mortality from recurrence ($p = .265$), or in all-cause mortality ($p = .209$)	160
Colon	LA (peridural)	Eight hundred and seventy-six patients involved (208 peridural)	Do not improve OS ($p = .175$), cancer-specific survival ($p = .111$) or DFS ($p = .43$)	161
Colon	Bupivacaine (epidural)	Two thousand seven hundred and forty-eight patients included (449 epidural)	No association between epidural and recurrence or death	162
Colon	LA (epidural)	Forty-two thousand one hundred and fifty-one patients included (9,670 epidural)	Association between epidural and improved survival (HR = 0.91, 95%CI[0.87–0.94]; $p < .001$)	138
Colo-rectal	LA (epidural)	Five hundred and eighty-eight patients involved (399 epidural).	Better five-year survival ($p = .01$)	3
Colo-rectal	LA (epidural)	Five hundred and nine patients enrolled (256 epidural).	Less recurrence in the subgroup of older patients ($p = .01$).	141
Colo-rectal	LA (epidural)	Six hundred and fifty-five patients included in two groups: epidural (n = 562) vs PCA (n = 93)	Reduction in all-cause mortality after rectal cancer surgery ($p = .049$).	142
Colo-rectal	LA (peridural)	Patients included into two groups (442 GA+peridural/ 307 GA alone)	Better 5-year survival ($p = .02$). HR for death decreased by 27%. In ASA 3–4 patients, significant greater survival ($p < .009$)	134
Colo-rectal	Bupivacaine (epidural)	Five hundred and ten patients involved (390 epidural)	Better 5-year RFS (HR = 0.74, 95%CI[0.56–0.95]; $p = .036$)	139
Colo-rectal	LA (epidural)	Two thousand nine hundred and eighty patients in each group after matching.	No benefit for mortality and recurrence.	163
Colo-rectal	Bupivacaine (epidural or spinal)	Four hundred and twenty-four patients included (107 epidural, 144 spinal, 173 PCA)	No difference in OS ($p = .622$) or DFS ($p = .49$) at 5 years	164
Colo-rectal	Bupivacaine (epidural)	Nine hundred and ninety-nine patients included (165 epidural)	No association between epidural and RFS or OS	165
Colo-rectal	Ropivacaine (epidural)	Two hundred and twenty-five patients included (92 epidural)	GA was associated with better outcomes	145
ENT	LA (epidural)	One hundred and seventy-one patients involved (111 epidural)	Increase DFS (HR = 0.49, 95%CI[0.25–0.96]; $p = .04$). Increase OS ($p = .03$)	143
Esophagus	Ropivacaine (epidural)	One hundred and fifty-three patients included (118 epidural)	No benefit in recurrence, 1-year mortality, or 5-year survival	166
Esophagus	LA (epidural)	One thousand nine hundred and twenty-one patients included (1,169 epidural)	Epidural improved 5-year survival ($p = .012$)	148
Esophagus	Ropivacaine (epidural)	Three hundred and fifty-six patients included (178 epidural)	Epidural decreased the incidence of pneumonia ($p = .008$), anastomotic leakage ($p = .029$), CRP level ($p = .044$). No benefits in recurrence ($p = .47$) or OS ($p = .46$)	149
Gastric	LA (epidural)	Two thousand seven hundred and forty-five patients (766 epidural)	No benefits in recurrence or survival	167
Gastric	Ropivacaine (epidural)	Three thousand seven hundred and ninety-nine patients included (3,425 epidural)	No benefits in recurrence ($p = .471$) or mortality ($p = .138$)	181
Gastric	Ropivacaine or levobupivacaine (epidural)	Two hundred and seventy-three patients included (157 epidural)	Greater long-term survival among younger patients<64 years-old ($p = .042$)	150
Gastric	LA (epidural)	One hundred and ninety-four patients included (97 epidural)	No benefit in survival ($p = .147$)	168
Gastro-esophageal	Bupivacaine (epidural)	One hundred and forty patients involved with epidural (n = 97) or not (n = 43).	Less recurrence ($p = .01$). Increased time to recurrence (HR = 0.33, 95%CI[0.17–0.63]; $p < .0001$). Better OS (HR = 0.42; 95%CI[0.16–0.75]; $p = .005$). Improved median time to death ($p = .029$)	140
Liver	Lidocaine (local injection)	Four hundred and eighty-nine patients involved (245 local injection).	Less recurrence ($p = .0022$). Less mortality ($p = .036$)	137
Liver	Bupivacaine (epidural)	Seven hundred and forty-four patients included (435 epidural)	No association between epidural and recurrence or mortality	169
Liver	Ropivacaine (epidural)	Eight hundred and nineteen patients included (451 epidural)	More recurrence ($p = .036$) and more death ($p = .003$) with epidural. No impact on RFS ($p = .509$)	156
Lung	Bupivacaine or ropivacaine (epidural)	Four hundred and forty-five patients involved (343 epidural /23 PCA/79 epidural + PCA)	No benefit in 2-year or 5-year RFS or OS	170

(Continued)

Table 1. (Continued).

Tumor surgery	Local anesthetic	Design	Results	Ref.
Lung	Bupivacaine (epidural)	Two thousand one hundred and ninety-one patients included (1,799 epidural)	No benefit in long-term mortality or OS	171
Melanoma	Bupivacaine (spinal anesthesia)	Two hundred and seventy-five patients included (52 spinal anesthesia + GA)	No benefit in survival ($p = .087$)	172
Ovary	LA (epidural)	One hundred eighty-two patients included (55 epidural).	Increased time to recurrence after surgery.	151
Ovary	Bupivacaine (neuraxial)	Eighty patients involved (37 epidural).	No benefit in OS or recurrence	173
Ovary	Lidocaine (intravenous)	Six hundred and four patients included after matching (302 lidocaine intravenous vs 302 without lidocaine)	Improved DFS ($p = .015$) and OS ($p = .042$)	147
Ovary	Bupivacaine or ropivacaine (epidural)	One hundred and forty-three patients included (106 epidural)	Better 3 – and 5-year OS (HR = 1.214; $p = .043$)	135
Ovary	LA (epidural)	One hundred and ninety-four patients included (60 epidural)	Less recurrence ($p = .028$). Longer DFS was associated with more than 48 h of epidural	152
Ovary	LA (epidural)	Six hundred and forty-eight patients included (435 epidural)	Better PFS ($p = .021$) and OS ($p < .001$). Epidural is independently associated with a decreased risk of progression (HR = 1.327, 95%CI[1.066–1.653]) and death (HR = 1.588, 95%CI[1.224–2.06])	153
Ovary	Ropivacaine (epidural)	One hundred and four patients included (51 epidural)	No benefits in DFS or OS	174
Pancreas	Lidocaine (intravenous)	Two thousand two hundred and thirty-nine patients involved. After propensity score: lidocaine (n = 915) or not (n = 915)	Benefit in 1-year OS ($p < .001$) and 3-year OS ($p = .011$). Lidocaine was associated with prolonged OS (HR = 0.616; 95%CI[0.29–0.783]; $p = .013$)	136
Pancreas	Ropivacaine (epidural)	Two hundred and fifteen patients included. 11 patients with high concentration of LA (0.375–0.5%) and 96 patients with low concentration (0.15–0.25%)	High concentration of ropivacaine improved OS ($p = .04$) and was an independent good prognostic factor (HR = 0.65, 95%CI[0.44–0.94]; $p = .03$)	154
Pancreas	Bupivacaine (epidural)	Two hundred and fifty-two patients included (n = 88 epidural; n = 164 without epidural)	No association with greater recurrence ($p = .87$) or all-cause mortality ($p = .85$).	175
Pancreas	Ropivacaine (peridural)	Ninety-eight patients included (70 peridural)	No benefits in recurrence or OS	176
Prostate	Bupivacaine (epidural)	One hundred and forty-eight patients involved (67 epidural)	Do not reduce the risk of progression. Do not improve survival.	177
Prostate	LA (epidural)	Two hundred and twenty-five patients included (102 epidural)	Lower risk of recurrence ($p = .012$)	1
Prostate	Bupivacaine (epidural)	Two hundred and sixty-one patients included (103 epidural)	Benefit in PFS (HR = 0.45; $p = .002$)	144
Prostate	LA (epidural)	One thousand one hundred and eleven patients included (578 epidural)	No benefit	178
Prostate	LA (epidural)	Ninety-nine patients included (49 epidural)	No benefit in recurrence (HR = 1.33, 95%CI[0.64–2.77]; $p = .44$)	179
Rectum	Bupivacaine (epidural)	One thousand two hundred and eighty-two patients included (237 epidural)	No association with RFS ($p = .491$) or OS ($p = .984$) or cancer-specific survival ($p = .482$)	180

Abbreviations: ASA, American society of anesthesiologists (physical status score); CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; GA, general anesthesia; HR, hazard ratio; LA, local anesthetics; PCA, patient-controlled analgesia; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival

Table 2. Meta-analyses investigating the oncological impact of local anesthetics.

Tumor surgery	Local anesthetic	Design	Results	Ref.
Solid tumors	LA (epidural)	Ten studies (=3,254 patients) included.	Subgroups with prostate cancer or follow-up less than or equal to two years (OR = 0.66, 95%CI[0.46–0.95], $p = .027$; OR = 0.70, 95%CI[0.51–0.98], $p = .035$; respectively) for recurrence and metastasis rate	183
Solid tumors	LA (regional anesthesia)	Twenty studies	Improve OS (HR = 0.84; 95%CI[0.75–0.94]; $I^2 = 41\%$] No reduction in recurrence (HR = 0.91, 95%CI[0.70–1.18; $I^2 = 83\%$]	184
Solid tumors	LA (neuraxial)	Twenty-one studies involved (15,160 patients with neuraxial anesthesia and 36,460 with GA)	Improved OS (HR = 0.853, 95%CI[0.741–0.981]; $p = .026$) Improve RFS (HR = 0.846, 95%CI[0.718–0.998]; $p = .047$)	185
Solid tumors	LA (epidural)	Fourteen studies (47,000 patients) included	Improved OS ($p = .013$)	182

Abbreviations: CI, confidence interval; GA, general anesthesia; HR, hazard ratio; LA, local anesthetics; OR, odds ratio; OS, overall survival; RFS, recurrence-free survival

2.2. Prospective studies

Twenty-eight prospective randomized controlled trials have investigated whether the use of LAs improves oncological outcomes (Table 3). Thirteen of these studies did not show significant differences between the treatment groups.[179,186–197] However, 50% of the published trials reported positive benefits in various solid tumors.

For instance, Guerrero Orriach et al. demonstrated in their study that epidurally administered ropivacaine, in association with intravenous hypnotics and lidocaine, increased DFS in a group of 100 patients with bladder cancer undergoing surgical procedures, as compared with the control group anesthetized with volatile hypnotics and opioids.[198] Christopherson et al. observed similar results after comparing colectomy performed under general anesthesia with isoflurane and fentanyl, with or without epidural bupivacaine.[199] In the study by Alexa et al., a significant reduction in recurrences was observed after the intravenous injection of lidocaine during colectomy.[200] After hepatectomy, the analgesic infusion of ropivacaine (bolus plus continuous injection through a local catheter) improved postoperative survival compared to the use of tramadol and fentanyl to control surgical pain.[201] The perfusion of ropivacaine through an intraperitoneal catheter minimized the time to initiate adjuvant chemotherapy after ovariectomy compared to the control group.[202] Finally, the recent multicenter randomized controlled trial by Badwe et al., including 1583 patients, showed significantly better OS and DFS, with or without recurrence, after the use of locally injected lidocaine in peritumoral tissue before the removal of breast tumors.[203]

Interestingly, indirect effects on the immune system were also observed. The serum of patients receiving LA during oncological surgery involved more active lymphocytes capable of inhibiting the proliferation of cancer cells in vitro.[105,204,205] Several ancillary studies reported a significant decrease in the pro-tumor inflammatory cytokines IL-6, while there was an increase in the anti-tumor IFN-γ.[105,115,206,207] Lower levels of VEGF, tumor growth factor-β (TGF-β), and cortisol in plasma were also observed in cases of ropivacaine injection through epidural, intraperitoneal or paravertebral routes, suggesting both a local impact (perhaps by slowing down the secretion of growth factors by the surrounding tumor tissue) and a systemic impact (perhaps by decreasing glucocorticoid stress).[118,206,208,209]

3. Future investigation

3.1. Completed trials

Numerous prospective randomized controlled trials have been initiated following the publication of the aforementioned preclinical studies, with the primary goal of confirming the data (Table 4). Most of the completed or terminated trials aim to evaluate whether the use of LAs with various modes of administration during the removal of primary breast, colorectal, liver, or lung cancer improves OS and/or DFS and hence decreases the incidence of recurrence (NCT01204242; NCT00418457; NCT03117894; NCT01231204; NCT01318161; NCT02801409; NCT01179308; NCT02256228; NCT02012244).

Many interventional trials were designed to investigate the control of acute/chronic postoperative pain by LA and explore a potential link with cancer outcomes (NCT01204242; NCT04390698; NCT03117894; NCT01231204; NCT01318161; NCT02012244; NCT02801406; NCT01179308). Several clinical trials include an ancillary study to evaluate the role of LA on the level and activity of immune cells collected from the blood of patients (NCT01716065, NCT04510935, NCT02801409, NCT01179308, NCT01367418, NCT01929915) or assess their impact on the proliferation and migration of cancer cells (NCT03594188; NCT04510935).

Five trials (NCT01318161; NCT02012244; NCT04510935; NCT02256228; NCT01367418) are investigating whether LA decreases the surgery-induced inflammatory response by assessing the levels of pro-inflammatory and pro-tumor cytokines (IL-2, IL-6, TNF-α).

Finally, the trial NCT00418457 has published results. In this multicenter randomized controlled trial, 2132 women undergoing breast cancer surgery were enrolled and allocated either to a general anesthesia group with volatiles and opioids or to a regional anesthesia-analgesia group, including paravertebral block plus intravenous hypnotic. Both groups were homogeneous for the characteristic baseline of patients, tumor, and surgical information. The regional administration of LA did not reduce the recurrence of cancer compared to the general group, and no association between baseline factors and the different types of anesthesia on recurrence was found.

3.2. Ongoing trials

Several randomized trials are currently investigating the effects of LAs administered through various routes on the activity of key antitumor immune effectors (Table 5). The study NCT02669186 aims to analyze the impact of bupivacaine on NK cytotoxicity. Here, bupivacaine is injected with or without fentanyl through epidural administration, which is distant from the tumor site and induces minimal serum concentrations of the LA. In the study NCT01841294, NK activity is measured after an intravenous lidocaine infusion, promoting 100% bioavailability of the LA and high tumor perfusion. Trials NCT01588847 and NCT05470166 are also focused on changes in the quantity of different immune cells (NK cells, T-cells, B-cells, activated thrombocytes) after the injection of bupivacaine alone through spinal anesthesia compared with general anesthesia involving a mix of intravenous and volatile hypnotics.

The phase 1 trial NCT04162535 is evaluating whether the anesthetic agents used during colorectal tumor removal induce antiproliferative effects. Here, patient serum containing various concentrations of anesthetics and different levels of immune effectors is tested in vitro on HCT116 human colon carcinoma cells.

Three studies focus on immune and genome changes induced by LAs. The early phase 1 study NCT04048278 assesses whether intravenous lidocaine can modify the activity of the oncogenic kinase SRC involved in the proliferation and survival of circulating tumor cells and the regulation of gene expression. Trials NCT04657237 and NCT03779685 investigate whether paravertebral block, used to control surgical and postoperative pain during mastectomy, induces changes in the

Table 3. Prospective randomized controlled trials investigating the oncological outcomes of local anesthetics.

Tumor surgery	Local anesthetic	Design	Results	Ref.
Bladder	Ropivacaine + lidocaine (epidural)	One hundred patients included (50 with epidural)	Longer DFS ($p = .02$)	198
Breast	Levobupivacaine (paravertebral)	Twenty-two patients randomized to receive propofol/paravertebral or sevoflurane/opioid	The serum of patients from the group paravertebral inhibits the proliferation of ER-MDA-MB-231 breast cancer cells *in vitro*.	204
Breast	Bupivacaine (paravertebral)	Forty patients randomized to receive paravertebral block or not.	Less increase in IL-6. Higher level in IFN-γ.	115
Breast	Ropivacaine (paravertebral)	One hundred and eighty patients randomized to receive paravertebral block or not.	Do not decrease recurrence or mortality	187
Breast	Ropivacaine (paravertebral)	Sixty patients involved to receive paravertebral block or not.	Do not decrease recurrence	188
Breast	Ropivacaine+ lidocaine (local injection)	Fifty-six patients randomized to receive local anesthesia or GA	Higher total lymphocytes number in GA group ($p = .04$)	205
Breast	Lidocaine (peritumoral)	One thousand five hundred and eighty-three patients randomized to receive lidocaine (n = 796) or not (n = 804)	Better 5-year DFS (HR = 0.74, 95%CI[0.58–0.95]; $p = .017$) and OS (HR = 0.71, 95%CI[0.53–0.94]; $p = .019$)	203
Breast	LA (paravertebral)	Two thousand one hundred and eight patients included (1,043 with paravertebral block)	No difference between groups	189
Cervix	Lidocaine (bolus and continuous intravenous infusion)	Thirty women randomized to receive lidocaine iv or normal saline.	Increase in the proliferation of lymphocytes. Decrease in apoptosis of lymphocytes. Better level of INF-γ	105
Colon	Bupivacaine (epidural)	One hundred and seventy-seven patients randomized to receive epidural or not.	Epidural improved survival before 1.46 years ($p = .012$)	199
Colon	Ropivacaine (epidural)	Forty patients randomized to receive epidural or not.	Decreased in VEGF ($p = .001$), TGF-β ($p = .027$) and IL-6 ($p = .007$). Increased in IL-10 ($p = .001$).	206
Colon	Ropivacaine (intraperitoneal catheter)	Thirty-seven patients randomized to receive LA through intraperitoneal catheter (n = 19) or not (n = 18).	No benefit in OS or all-cause mortality. Higher rate of cancer-specific mortality ($p < .046$)	190
Colo-rectal	Ropivacaine (intraperitoneal catheter)	Sixty patients included (30 with infiltration)	No effect on NK cytotoxicity, recurrence or metastases	191
Colo-rectal	LA (epidural)	One hundred and eighty patients randomized to receive epidural (n = 89) or PCA (n = 91).	No significant difference for DFS at 5 years	192
Colo-rectal	Lidocaine (intravenous)	Eighty-two patients randomized to receive lidocaine or not with or without ketamine.	No influence on inflammatory markers.	197
Colo-rectal	Lidocaine (intravenous)	One hundred and fifty patients randomized to receive lidocaine (n = 77) or not (n = 73).	Decreased rate of recurrence ($p = .03$) but no impact on 1-year survival ($p = .22$)	200
ENT	Ropivacaine (epidural)	Thirty patients randomized to receive epidural or not.	Reduction in blood glucose ($p = .0153$) and cortisol ($p = .0074$)	118
Gastric	Ropivacaine (epidural)	Fifty patients randomized to receive epidural or not.	Increased in IFN-γ. Less increase in IL-6.	207
Liver	Ropivacaine (bolus+ infiltration)	Sixty patients included (20 with tramadol, 20 with ropivacaine, 20 with fentanyl)	Ropivacaine increased survival ($p = .029$)	201
Lung	Ropivacaine (paravertebral)	Forty patients involved to receive paravertebral/propofol *vs* sevoflurane	Lower VEGF and TGF-β concentration ($p < .05$)	208
Lung	Ropivacaine (paravertebral)	One hundred and fifty-nine patients randomized to receive ropivacaine (10 mg or 25 mg or 50 mg)	No influence on OS	193
Lung	Ropivacaine (epidural)	Four hundred patients included (200 with epidural)	No benefits in RFS or OS	194
Ovary	Ropivacaine (intraperitoneal catheter)	Forty patients randomized to have intraperitoneal catheter of LA or not	Serum cortisol was lower in LA group ($p = .023$)	209
Ovary	Ropivacaine (intraperitoneal catheter)	Forty women involved to receive intraperitoneal catheter or not.	Reduction of time to initiate chemotherapy after surgery ($p = .021$)	202
Pancreas	Lidocaine (intravenous)	Five hundred and sixty-three patients randomized to receive lidocaine intravenous (n = 283) or not (n = 280)	No association with better OS ($p = .79$) or DFS ($p = .44$)	195
Prostate	Ropivacaine (epidural)	Ninety-nine patients randomized to receive epidural/GA or GA alone.	No difference in DFS.	179
Solid tumors	Bupivacaine or Ropivacaine (epidural)	Four hundred and forty-six patients included (230 with epidural)	No benefits in DFS	186
Solid tumors	Ropivacaine (epidural)	One thousand seven hundred and twelve patients included (853 with epidural)	No benefits in OS	196

Abbreviations: DFS, disease-free survival; GA, general anesthesia; HR, hazard ratio; iv, intravenous; IFN, interferon; IL, interleukin; LA, local anesthetic; NK, natural killer cells; OS, overall survival; PCA, patient-controlled analgesia; RFS, recurrence-free survival; TGF, tumor growth factor; VEGF, vascular endothelial growth factor

Table 4. Completed and terminated prospective trials investigating the oncological outcomes of local anesthetics.

Tumor surgery	Local anesthetic	Administration route	Oncological endpoints	Potential endpoints related to cancer outcome	Phase	Status	Ref.
Breast	Lidocaine	Intravenous	5-year recurrence	Chronic pain Opioid use	2	completed	NCT01204242
Breast	LA	Epidural or Regional (paravertebral)	10-year recurrence	Postsurgical pain Neuropathic pain	3	completed	NCT00418457
Breast	LA	Regional	Circulating tumor cells, level of cytokines, breast cancer antibodies, dendritic cells, T, B and NK cells		Obser-vational	completed	NCT01716065
Breast	Ropivacaine *vs* lidocaine	Regional (paravertebral)	Recurrence up to 12 months	Postoperative pain	NA	completed	NCT04390698
Breast	Ropivacaine	Regional	Mortality 3 – and 5-year recurrence	Opioid use, actual/ chronic pain	NA	completed	NCT03117894
Breast	Ropivacaine	Regional (continuous infusion for 3 days)	3-year cancer recurrence	Opioid use Pain	4	completed	NCT01231204
Colo-rectal	Ropivacaine	Epidural	5-year mortality 7-year recurrence	Inflammation (perioperative cytokine concentration in blood), postoperative pain	3	terminated	NCT01318161
Colo-rectal	Ropivacaine	Infiltration	1-year recurrence, NK cell activity	Inflammatory responses, IL-2 level	NA	completed	NCT02012244
Liver	Lidocaine	Sub-cutaneous	Percentage change from post – to pre-operative values of HepG2 cells; Invasion, migration and proliferation of HepG2 cells cultured in patients' serum	IL-1β, IL-6, TNF-α, IFN-γ and IL-2 level	NA	completed	NCT04510935
Liver	LA	Local	Cell proliferation Cell migration and metastasis		NA	completed	NCT03594188
Lung	LA	Epidural	4-year RFS, mortality, OS, number of CD8$^+$ and Treg in tumor, percentage of NK and T-cell in blood	Pain	NA	completed	NCT02801409
Lung	LA	Epidural	5-year disease-free survival, NK cell function, immune function markers,	Pain	NA	terminated	NCT01179308
Ovary	Ropivacaine	Intraperitoneal	PFS, morbidity	Inflammatory markers, opioid use, pain	3	completed	NCT02256228
Pancreas	Bupivacaine	Epidural	Immunoprofile (CD4$^+$, CD8$^+$, CD19$^+$, NK, DC, Treg), 1-year survival		NA	completed	NCT01929915
Prostate	Bupivacaine + ropivacaine	Epidural	NK activity	Release of IL-2, IL-6, TNF-α, cortisol	3	completed	NCT01367418

Abbreviations: DC, dendritic cell; IFN, interferon; IL, interleukin; LA, local anesthetics; NA, non-applicable; NK, natural killer; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; TNF, tumor necrosis factor; Treg, regulatory T cells

transcriptome, impacts immune progenitors, and specifically disturbs the expression of PD-1 and programmed cell death (ligand) protein 1(PD-L1) on blood monocyte cells.

Interestingly, many ongoing studies are exploring factors that might indirectly influence oncological outcomes. Three prospective trials (NCT04162535; NCT04449289; NCT03134430) plan to assess the serum concentration of anesthetics to find an association with cancer progression. Several studies are designed to measure pain and opioid consumption, which may encourage tumor growth and recurrence (NCT00938171; NCT05494502; NCT04657237; NCT02786329; NCT01841294; NCT02840227; NCT05470166; and NCT03134430). The phase 3 trial NCT04065009 is evaluating whether the use of LA influences the time to start adjuvant chemotherapy after surgery. Finally, most ongoing research is also examining the effect of LAs on RFS and OS (NCT03597087; NCT04638569; NCT00938171; NCT05494502; NCT03779685; NCT04162535; NCT02786329; NCT02474511; NCT03813953; NCT02474511; NCT02840227; NCT01588847; NCT04449289 and NCT03134430).

Discussion

The past two decades have witnessed a growing number of articles examining the role of LAs in oncological outcomes. Preclinical studies have consistently demonstrated the anti-tumor actions of both ester and amide type LAs across various tumor types. Notably, prilocaine and chloroprocaine, although acting quickly, are less investigated, possibly due to their short duration of action, which might render them less efficient on malignant cells.

Although the direct anti-tumor action of LAs appears straightforward, understanding how LAs may exert anti-tumor effects after injection far from the tumor site is more complex. Indeed, locally injected LAs are close to the tumor bed, hence favoring the control of the residual malignant cells before migration. Through continuous intravenous injection, LAs can propagate through the systemic circulation, ensuring a stable diffusion throughout the entire tumor and the circulating tumor cells disseminated during the surgical intervention. The potential positive effects of spinal or epidural

Table 5. Ongoing prospective trials investigating the oncological outcomes of local anesthetics.

Tumor surgery	Local anesthetic	Administration	Oncological endpoints	Other endpoints potentially related to cancer outcome	Phase	Status	Ref.
Abdominal tumor	Bupivacaine	Epidural	NK cytotoxicity		NA	enrolling by invitation	NCT02669186
Bladder	Bupivacaine	Spinal	2-year RFS, 2-year PFS		NA	unknown	NCT03597087
Bladder	Bupivacaine	Regional (obturator nerve block)	Recurrent tumor at 3 months		NA	recruiting	NCT04638569
Breast	Lidocaine + bupivacaine	Tumor site	5-year DFS	Pain, opioid use	3	unknown	NCT00938171
Breast	Lidocaine	Peri-tumoral	5-year DFS, 5-year OS		3	not yet recruiting	NCT01916317
Breast	Ropivacaine	Regional (erector spinae plane)	3-year PFS, 3-year OS	Chronic pain, neuropathic pain	NA	not yet recruiting	NCT05494502
Breast	LA	Regional (paravertebral)	Genome expression by microarray, immune progenitors, 7-year RFS, 7-year OS		NA	unknown	NCT03779685
Breast	Bupivacaine	Regional (paravertebral)	Change in level of PD-1 and PD-L1 on peripheral blood monocyte cells	Total analgesia (paracetamol)	NA	unknown	NCT04657237
Colo-rectal	Lidocaine	Intravenous	Antiproliferative and apoptotic effects of anesthetics, evaluation of patient serum on colon cancer cell culture (HCT116), 5-year survival	Lidocaine concentration	1	recruiting	NCT04162535
Colo-rectal	Lidocaine	Intravenous	5-year survival, 5-year recurrence	Pain, opioid use	Early 1	recruiting	NCT02786329
Colo-rectal	Lidocaine	Intravenous	NK activity	Pain, opioid use	4	unknown	NCT01841294
Glio-blastoma	LA	Local	Morbidity, resection percentage, progression-free survival, OS, residual tumor volume		Obser-vational	recruiting	NCT04708171
Liver	LA	Infiltration vs epidural	3 – and 5-year OS, 5-year DFS		NA	unknown	NCT03813953
Liver	LA	Local	3-year recurrence		Obser-vational	unknown	NCT02474511
Lung	LA	Epidural	3-year DFS	Pain, opioid use	NA	not yet recruiting	NCT02840227
Melanoma	Bupivacaine	Spinal	OS, change of total amount of immune cells (T-, B-, NK-cells), changes in TGF-β, activation of thrombocytes, potential predictive biomarkers		NA	unknown	NCT01588847
Ovary	Ropivacaine	Intraperitoneal	Time to start of adjuvant chemotherapy after surgery, 3-5-year survival, morbidity		3	recruiting	NCT04065009
Pancreas	Lidocaine	Intravenous	NK level, lymphocytes level	Pain, analgesic consumption	NA	recruiting	NCT05470166
Pancreas	Lidocaine	Intravenous	Src tyrosine kinase activity in circulating tumor cells, cytokine/chemokine levels in serum, regulation of gene expression, circulating tumor cells		Early 1	recruiting	NCT04048278
Pancreas	Lidocaine vs ropivacaine	Intravenous vs Epidural	1 – and 3-year recurrence, 1 – and 3-year survival after surgery	LA concentration	2	not yet recruiting	NCT04449289
Solid tumors	Ropivacaine + lidocaine	Regional	5-year recurrence, 5-year survival, percentage of immunocytes and cytokines	Intraoperative anesthetic level, pain	NA	not yet recruiting	NCT03134430

Abbreviations: DC, dendritic cell; DFS, disease-free survival; LA, local anesthetics; NA, non-applicable; NK, natural killer cells; OS, overall survival; PD(L)1, Programmed cell Death (Ligand) protein 1; PFS, progression-free survival; RFS, recurrence-free survival; TGF, tumor growth factor

administration are intriguing, and one hypothesis suggests that epidural anesthesia reduces glucocorticoid stress during oncological surgery. This stress, triggered by local inflammatory pain, releases pro-inflammatory, pro-tumor cytokines, cortisol and catecholamines, promoting the proliferation, migration and invasiveness of cancer cells.[210–213]

Controlled pain and inflammation, through optimal pain control, may enhance the capacity of the immune system to mount anticancer responses, as indicated by increased release of IFN-γ. Moreover, by inducing a partial ICD response, LA may stimulate cytotoxic T lymphocytes (CTLs) and generate immune memory to control residual circulating malignant cells and decrease recurrence incidence.[214–217] Preclinical results suggested that intratumoral lidocaine and ropivacaine influence the tumor microenvironment by increasing activated CD8$^+$ T cells and decreasing immunosuppressive cells such as FOXP3$^+$ Tregs, hence reenforcing immunosurveillance and preventing metastatic spread.[218,219] This may also sensitize to immunotherapy with PD-1 blocking antibodies.[220–222]

While preclinical studies provide robust evidence for the anti-tumor effects of LAs, clinical studies face several challenges in translating these results. Many published trials lack power, with observational and retrospective designs often hampered by an imbalance in study groups.[181] A number of confounding factors such as heterogeneity in disease stage, variations in (neo)-adjuvant immunomodulatory treatments, cancer aggressiveness and the concurrent use of pro-tumor agents, further complicate the interpretation of results. The mode of LA administration, with variations in injection duration and methods, is also debated. Additional confounding factors such as undernutrition, anemia, inflammation, pain, and stress are often not optimally controlled.

Despite these challenges, subgroup analyses suggest that specific patient groups or tumor types may be particularly susceptible to the beneficial actions of LAs. However, recent well-designed trials have provided contrasting results. Sessler *et al.*'s study found no reduction in breast cancer recurrence with paravertebral block compared to the control group, possibly due to the anti-tumor properties of the volatile hypnotic sevoflurane that was used in the control group.[223–225] In contrast, Badwe *et al.*'s trial showed a significant increase in DFS and OS in the lidocaine group, supporting a potential direct cytolytic effect of lidocaine on breast tumor cells.[203] Of note, irrespective of the mode and duration of administration, LA did not induce side effects. Thus, further studies should focus on the safety and feasibility of different combination strategies such as LA plus chemotherapy and immunotherapy.[226] Future clinical trials should also explore whether LA cotreatment would allow reducing the toxicity of conventional anticancer agents. Another focus should be to use LAs for potentiating the anti-tumor immune response by stimulating immune effectors, modulating the tumor microenvironment and *in fine* rendering the tumors more sensitive to antineoplastic treatments.

Conclusion

Attempts are underway to clinically translate promising preclinical data on the potential antitumor and immuno-modulatory properties of local anesthetics (LAs). This endeavor meets challenges due to several factors, such as the relatively modest therapeutically effects of LAs and the presence of various confounding biases. As a result, there is an urgent need for significant efforts to ameliorate the design of future clinical trials by reducing selection bias, increasing the number of inclusions and targeting patient populations that might benefit from LA interventions such as early-stage patients. Future investigations should explore the impact of LAs when used in combination with conventional anti-tumor agents, peri-operative but also as alongside the treatment. This comprehensive approach is crucial for gaining a deeper understanding of the potential benefits of LAs in the context of anticancer treatments. By refining study design, controlling confounding factors, and identifying optimal patient populations, clinician scientists might contribute to clarifying the role of LAs in improving oncological outcomes.

Abbreviations

ATF4	activating transcription factor 4
ATF6	activating transcription factor 6
ATP	adenosine triphosphate
CDK	cyclin-dependent kinase
CHOP	C/EBP homologous protein
circRNA	circular RNA
CPEB3	cytoplasmic polyadenylation element-binding protein 3
CYTC	cytochrome C
DAMPs	danger associated molecular patterns
DC	dendritic cell
DFS	disease-free survival
DNMTs	DNA methyltransferases
EGFR	epithelial growth factor receptor
EIF2alpha	eukaryotic initiation factor 2 alpha
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinases
GA	general anesthesia
HB-EGF	heparin-binding epidermal growth factor-like growth factor
HIF	hypoxia-inducible factor
HMGB1	high mobility group box 1
ICD	immunogenic cell death
ICU	intensive care unit
IFN	interferon
IL	interleukin
IRE1	inositol-requiring enzyme 1
KAT8	lysine acetyltransferase 8
LA	local anesthetics
LC3B	lipidation of autophagy-related protein light-chain 3B
lncRNA	long non-coding RNA
MAPK	mitogen-activated protein kinase
MEG	maternally expressed gene
miRNA	microRNA
MMP	matrix metalloproteinase
NA	non-applicable
NK	natural killer
NF-kB	nuclear factor-kappa B
OGFRP1	opioid growth factor receptor pseudogene 1
OS	overall survival
PARP	poly ADP-ribose polymerase
PCS/MCS	Physical and Mental Health Composite Scores
PD(L)1	Programmed cell Death (Ligand) protein 1
PERK	protein kinase RNA-like endoplasmic reticulum kinase

PI3K/Akt/Mtorc	phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin complex
PONV	postoperative nausea and vomiting
RAC1/JNK/paxillin/FAK	RAS-related C3 botulinum toxin substrate 1/ c-JUN N-terminal kinase/paxillin/focal adhesion kinase
RHO-A/ROCK/MLC	RHO-associated protein kinase/myosin light chain
RFS	recurrence-free survival
Src	Src protein tyrosine kinase
STAT3	Signal transducer and activator of transcription 3
Th	T helper cells
TGF	tumor growth factor
TIVA	total intravenous anesthesia
TNF	tumor necrosis factor
Treg	regulatory T cells
TRPM7	transient receptor potential melastatin 7
VEGF	vascular endothelium growth factor
WIF-1	Wnt inhibitory factor-1
YAP	Yes-associated protein 1
XBP1	X-box binding protein 1

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References

1. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiol. 2008;109 (2):180–187. doi:10.1097/ALN.0b013e31817f5b73.
2. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiol. 2006;105(4):660–664. doi:10.1097/00000542-200610000-00008.
3. Vogelaar FJ, Abegg R, van der Linden Jc, Cornelisse HG, van Dorsten Fr, Lemmens VE, Bosscha K, van der Linden JC, van Dorsten FRC. Epidural analgesia associated with better survival in colon cancer. Int J Colorectal Dis. 2015;30(8):1103–1107. doi:10.1007/s00384-015-2224-8.
4. Li T, Chen L, Zhao H, Wu L, Masters J, Han C, Hirota K, Ma D. Both Bupivacaine and Levobupivacaine inhibit colon cancer cell growth but not melanoma cells in vitro. J Anesth. 2019;33(1):17–25. doi:10.1007/s00540-018-2577-6.
5. Tat T, Jurj A, Selicean C, Pasca S, Ionescu D. Antiproliferative effects of propofol and lidocaine on the colon adenocarcinoma microenvironment. J BUON. 2019;24:106–115.
6. 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 Anesthesiol. 2020;20 (1):126. doi:10.1186/s12871-020-01039-1.
7. Castelli V, Piroli A, Marinangeli F, d'Angelo M, Benedetti E, Ippoliti R, Zis P, Varrassi G, Giordano A, Paladini A, et al. Local anesthetics counteract cell proliferation and migration of human triple-negative breast cancer and melanoma cells. J Cell Physiol. 2020;235(4):3474–3484. doi:10.1002/jcp.29236.
8. Zuckerman LM, Frames WL, Mirshahidi HR, Williams NL, Shields TG, Otoukesh S, Mirshahidi S. Antiproliferative effect of bupivacaine on patient-derived sarcoma cells. Mol Clin Oncol. 2020;13 (3):7. doi:10.3892/mco.2020.2077.
9. Mammoto T, Higashiyama S, Mukai M, Mammoto A, Ayaki M, Mashimo T, Hayashi Y, Kishi Y, Nakamura H, Akedo H. Infiltration anesthetic lidocaine inhibits cancer cell invasion by modulating ectodomain shedding of heparin-binding epidermal growth factor-like growth factor (HB-EGF). J Cell Physiol. 2002;192(3):351–358. doi:10.1002/jcp.10145.
10. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, Buggy DJ. Effect of perioperative lidocaine on metastasis after sevoflurane or ketamine-xylazine anaesthesia for breast tumour resection in a murine model. Br J Anaesth. 2018;121 (1):76–85. doi:10.1016/j.bja.2017.12.043.
11. Wall TP, Crowley PD, Sherwin A, Foley AG, Buggy DJ. Effects of lidocaine and src inhibition on metastasis in a murine model of breast cancer surgery. Cancers (Basel). 2019;11(10):1414. doi:10.3390/cancers11101414.
12. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, Buggy DJ. Effect of perioperative lidocaine, propofol and steroids on pulmonary metastasis in a murine model of breast cancer surgery. Cancers. 2019;11(5):613. doi:10.3390/cancers11050613.
13. Liu C, Yu M, Li Y, Wang H, Xu C, Zhang X, Li M, Guo H, Ma D, Guo X. Lidocaine inhibits the metastatic potential of ovarian cancer by blocking Na(V) 1.5-mediated EMT and FAK/Paxillin signaling pathway. Cancer Med. 2021;10(1):337–349. doi:10.1002/cam4.3621.

14. D'Agostino G, Saporito A, Cecchinato V, Silvestri Y, Borgeat A, Anselmi L, Uguccioni M. Lidocaine inhibits cytoskeletal remodelling and human breast cancer cell migration. Br J Anaesth. 2018;121(4):962–968. doi:10.1016/j.bja.2018.07.015.

15. Yin D, Liu L, Shi Z, Zhang L, Yang Y. Ropivacaine inhibits cell proliferation, migration and invasion, whereas induces oxidative stress and cell apoptosis by circSCAF11/miR-145-5p axis in glioma. Cancer Manag Res. 2020;12:11145–11155. doi:10.2147/CMAR.S274975.

16. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, Martin SS. Local anesthetics inhibit kinesin motility and microtentacle protrusions in human epithelial and breast tumor cells. Breast Cancer Res Treat. 2011;129(3):691–701. doi:10.1007/s10549-010-1239-7.

17. Xing B, Yang L, Cui Y. Lidocaine inhibited migration of NSCLCA549 cells via the CXCR4 regulation. Cancer Biomark. 2022;33(3):317–330. doi:10.3233/CBM-210249.

18. Leng T, Lin S, Xiong Z, Lin J. Lidocaine suppresses glioma cell proliferation by inhibiting TRPM7 channels. Int J Physiol Pathophysiol Pharmacol. 2017;9:8–15.

19. Liu H, Dilger JP, Lin J. Lidocaine suppresses viability and migration of human breast cancer cells: TRPM7 as a target for some breast cancer cell lines. Cancers. 2021;13(2). doi:10.3390/cancers13020234.

20. Sun M, Huang S, Gao Y. Lidocaine inhibits the proliferation and metastasis of epithelial ovarian cancer through the Wnt/beta-catenin pathway. Transl Cancer Res. 2021;10(7):3479–3490. doi:10.21037/tcr-21-1047.

21. Dan J, Gong X, Li D, Zhu G, Wang L, Li F. Inhibition of gastric cancer by local anesthetic bupivacaine through multiple mechanisms independent of sodium channel blockade. Biomedicine Pharmacotherapy. 2018;103:823–828. doi:10.1016/j.biopha.2018.04.106.

22. Zhang Y, Peng X, Zheng Q. Ropivacaine inhibits the migration of esophageal cancer cells via sodium-channel-independent but prenylation-dependent inhibition of Rac1/JNK/paxillin/FAK. Biochem Biophys Res Commun. 2018;501(4):1074–1079. doi:10.1016/j.bbrc.2018.05.110.

23. 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):700–707. doi:10.1002/ddr.21671.

24. Wang X, Li T. Ropivacaine inhibits the proliferation and migration of colorectal cancer cells through ITGB1. Bioengineered. 2021;12(1):44–53. doi:10.1080/21655979.2020.1857120.

25. Piegeler T, Schlapfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD, Beck-Schimmer B. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNFalpha-induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. British J Anaesthesia. 2015;115(5):784–791. doi:10.1093/bja/aev341.

26. Shen J, Han L, Xue Y, Li C, Jia H, Zhu K. Ropivacaine Inhibits Lung Cancer Cell Malignancy Through Downregulation of Cellular Signaling Including HIF-1alpha In Vitro. Front Pharmacol. 2021;12:806954. doi:10.3389/fphar.2021.806954.

27. Haraguchi-Suzuki K, Kawabata-Iwakawa R, Suzuki T, Suto T, Takazawa T, Saito S. Local anesthetic lidocaine induces growth suppression of HeLa cells by decreasing and changing the cellular localization of the proliferation marker Ki-67. Genes Cells. 2022;27(11):675–684. doi:10.1111/gtc.12983.

28. Bezu L, Wu Chuang A, Sauvat A, Humeau J, Xie W, Cerrato G, Liu P, Zhao L, Zhang S, Le Naour J, et al. Local anesthetics elicit immune-dependent anticancer effects. J Immunotherapy Cancer. 2022;10(4):e004151. doi:10.1136/jitc-2021-004151.

29. Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. Anesth Analg. 2006;102(4):1103–1107. doi:10.1213/01.ane.0000198330.84341.35.

30. Ma XW, Li Y, Han XC, Xin QZ. The effect of low dosage of procaine on lung cancer cell proliferation. Eur Rev Med Pharmacol Sci. 2016;20:4791–4795.

31. Liu H, Wang Y, Chen B, Shen X, Li W. Effects of lidocaine-mediated CPEB3 upregulation in human hepatocellular carcinoma cell proliferation in vitro. Biomed Res Int. 2018;2018:8403157. doi:10.1155/2018/8403157.

32. Teng X, Liu Y, Wang L, Wang G. Lidocaine exerts anticancer activity in bladder cancer by targeting isoprenylcysteine carboxyl-methyltransferase (ICMT). Translational Andrology and Urology. 2021;10(11):4219–4230. doi:10.21037/tau-21-893.

33. 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.

34. Chen J, Jiao Z, Wang A, Zhong W. Lidocaine inhibits melanoma cell proliferation by regulating ERK phosphorylation. J Cell Biochem. 2019;120(4):6402–6408. doi:10.1002/jcb.27927.

35. Yang W, Cai J, Zhang H, Wang G, Jiang W. Effects of lidocaine and ropivacaine on gastric cancer cells through down-regulation of ERK1/2 phosphorylation in vitro. Anticancer Res. 2018;38(12):6729–6735. doi:10.21873/anticanres.13042.

36. Li C, Gao S, Li X, Li C, Ma L. Procaine inhibits the proliferation and migration of colon cancer cells through inactivation of the ERK/MAPK/FAK pathways by regulation of RhoA. Oncol Res. 2018;26(2):209–217. doi:10.3727/096504017X14944585873622.

37. Zhang L, Hu R, Cheng Y, Wu X, Xi S, Sun Y, Jiang H. Lidocaine inhibits the proliferation of lung cancer by regulating the expression of GOLT1A. Cell Prolif. 2017;50(5). doi:10.1111/cpr.12364.

38. Le Gac G, Angenard G, Clement B, Laviolle B, Coulouarn C, Beloeil H. Local anesthetics inhibit the growth of human hepatocellular carcinoma cells. Anesth Analg. 2017;125(5):1600–1609. doi:10.1213/ANE.0000000000002429.

39. Kwakye AK, Kampo S, Lv J, Ramzan MN, Richard SA, Falagan AA, Agudogo J, Atito-Narh E, Yan Q, Wen QP. Levobupivacaine inhibits proliferation and promotes apoptosis of breast cancer cells by suppressing the PI3K/Akt/mTOR signalling pathway. BMC Res Notes. 2020;13(1):386. doi:10.1186/s13104-020-05191-2.

40. Tada M, Imazeki F, Fukai K, Sakamoto A, Arai M, Mikata R, Tokuhisa T, Yokosuka O. Procaine inhibits the proliferation and DNA methylation in human hepatoma cells. Hepatol Int. 2007;1(3):355–364. doi:10.1007/s12072-007-9014-5.

41. 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):2748–2757. doi:10.21037/jtd.2016.09.66.

42. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, Xue RF, Yuan YF, Zeng WA. Lidocaine induces apoptosis and suppresses tumor growth in human hepatocellular carcinoma cells In vitro and in a xenograft model in vivo. Anesthesiol. 2017;126(5):868–881. doi:10.1097/ALN.0000000000001528.

43. Jose C, Hebert-Chatelain E, Dias Amoedo N, Roche E, Obre E, Lacombe D, Rezvani HR, Pourquier P, Nouette-Gaulain K, Rossignol R. Redox mechanism of levobupivacaine cytostatic effect on human prostate cancer cells. Redox Biol. 2018;18:33–42. doi:10.1016/j.redox.2018.05.014.

44. Zhang R, Lian Y, Xie K, Cai Y, Pan Y, Zhu Y. Ropivacaine suppresses tumor biological characteristics of human hepatocellular carcinoma via inhibiting IGF-1R/PI3K/AKT/mTOR signaling axis. Bioengineered. 2021;12(2):9162–9173. doi:10.1080/21655979.2021.1995103.

45. Wang L, Guo W, Guan H, Yan N, Cai X, Zhu L. Local anesthetic bupivacaine inhibits proliferation and metastasis of hepatocellular carcinoma cells via suppressing PI3K/Akt and MAPK signaling. J Biochem Mol Toxicol. 2021;35(10):e22871. doi:10.1002/jbt.22871.

46. Hao J, Zhang W, Huang Z. Bupivacaine modulates the apoptosis and ferroptosis in bladder cancer via phosphatidylinositol 3-kinase (PI3K)/AKT pathway. Bioengineered. 2022;13(3):6794–6806. doi:10.1080/21655979.2022.2036909.

47. Lu Y, Mao J, Xu Y, Pan H, Wang Y, Li W. Ropivacaine represses the ovarian cancer cell stemness and facilitates cell ferroptosis through inactivating the PI3K/AKT signaling pathway. Hum Exp Toxicol. 2022;41:9603271221120652. doi:10.1177/09603271221120652.

48. Lu J, Xu SY, Zhang QG, Xu R, Lei HY. Bupivacaine induces apoptosis via mitochondria and p38 MAPK dependent pathways. European J Pharmacol. 2011;657(1–3):51–58. doi:10.1016/j.ejphar.2011.01.055.

49. Chang YC, Hsu YC, Liu CL, Huang SY, Hu MC, Cheng SP, Jiang Y. 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.

50. Ye L, Zhang Y, Chen YJ, Liu Q. Anti-tumor effects of lidocaine on human gastric cancer cells in vitro. Bratisl Lek Listy. 2019;120 (3):212–217. doi:10.4149/BLL_2019_036.

51. Sun H, Sun Y. Lidocaine inhibits proliferation and metastasis of lung cancer cell via regulation of miR-539/EGFR axis. Artif Cells Nanomed Biotechnol. 2019;47(1):2866–2874. doi:10.1080/21691401.2019.1636807.

52. Okamoto A, Tanaka M, Sumi C, Oku K, Kusunoki M, Nishi K, Matsuo Y, Takenaga K, Shingu K, Hirota K. The antioxidant N-acetyl cysteine suppresses lidocaine-induced 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.

53. Li YC, Wang Y, Li DD, Zhang Y, Zhao TC, Li CF. Procaine is a specific DNA methylation inhibitor with anti-tumor effect for human gastric cancer. J Cell Biochem. 2018;119(2):2440–2449. doi:10.1002/jcb.26407.

54. Chang YC, Liu CL, Chen MJ, Hsu YW, Chen SN, Lin CH, Chen CM, Yang FM, Hu MC. Local anesthetics induce apoptosis in human breast tumor cells. Anesth Analg. 2014;118(1):116–124. doi:10.1213/ANE.0b013e3182a94479.

55. Mirshahidi S, Shields TG, de Necochea-Campion R, Yuan X, Janjua A, Williams NL, Mirshahidi HR, Reeves ME, Duerksen-Hughes P, Zuckerman LM. Bupivacaine and lidocaine induce apoptosis in osteosarcoma tumor cells. Clin Orthop Relat Res. 2021;479(1):180–194. doi:10.1097/CORR.0000000000001510.

56. Wang W, Zhu M, Xu Z, Li W, Dong X, Chen Y, Lin B, Li M. Ropivacaine promotes apoptosis of hepatocellular carcinoma cells through damaging mitochondria and activating caspase-3 activity. Bio Res. 2019;52(1):36. doi:10.1186/s40659-019-0242-7.

57. 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):455–462. doi:10.1002/cbf.3208.

58. 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 (1):26277. doi:10.1038/srep26277.

59. 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):186–192. doi:10.1016/j.jphs.2019.01.014.

60. Arita K, Utsumi T, Kato A, Kanno T, Kobuchi H, Inoue B, Akiyama J, Utsumi K. Mechanism of dibucaine-induced apoptosis in promyelocytic leukemia cells (HL-60). Bio Pharmacol. 2000;60 (7):905–915. doi:10.1016/s0006-2952(00)00406-8.

61. Liu B, Yan X, Hou Z, Zhang L, Zhang D. Impact of Bupivacaine on malignant proliferation, apoptosis and autophagy of human colorectal cancer SW480 cells through regulating NF-kappaB signaling path. Bioengineered. 2021;12(1):2723–2733. doi:10.1080/21655979.2021.1937911.

62. Long D, Fang X, Yuan P, Cheng L, Li H, Qu L. Lidocaine promotes apoptosis in breast cancer cells by affecting VDAC1 expression. BMC Anesthesiol. 2022;22(1):273. doi:10.1186/s12871-022-01818-y.

63. Chen JL, Liu ST, Huang SM, Wu ZF. Apoptosis, Proliferation, and Autophagy Are Involved in Local Anesthetic-Induced Cytotoxicity of Human Breast Cancer Cells. Int J Mol Sci. 2022;23(24):15455. doi:10.3390/ijms232415455.

64. Long D, Chen Y, Qu L, Dong Y. Lidocaine inhibits the proliferation and migration of endometrial cancer cells, and promotes apoptosis by inducing autophagy. Oncol Lett. 2022;24(4):347. doi:10.3892/ol.2022.13467.

65. Qiao H, Zhang W, Liu P, Zhu R, Zhang J, Gao J, Li T, Zhang J. Ropivacaine inhibits proliferation and invasion and promotes apoptosis and autophagy in bladder cancer cells via inhibiting PI3K/AKT pathway. J Biochem Mol Toxicol. 2023;37(1):e23233. doi:10.1002/jbt.23233.

66. Werdehausen R, Fazeli S, Braun S, Hermanns H, Essmann F, Hollmann MW, Bauer I, Stevens MF. Apoptosis induction by different local anaesthetics in a neuroblastoma cell line. Br J Anaesth. 2009;103(5):711–718. doi:10.1093/bja/aep236.

67. Mao SH, Zhu CH, Nie Y, Yu J, Wang L. Levobupivacaine Induces Ferroptosis by miR-489-3p/SLC7A11 Signaling in Gastric Cancer. Front pharmacol. 2021;12:681338. doi:10.3389/fphar.2021.681338.

68. Sun D, Li YC, Zhang XY. Lidocaine promoted ferroptosis by targeting miR-382-5p /SLC7A11 axis in ovarian and breast cancer. Front pharmacol. 2021;12:681223. doi:10.3389/fphar.2021.681223.

69. Meng M, Huang M, Liu C, Wang J, Ren W, Cui S, Gu J, Xie J, Ma B, Yang G, et al. Local anesthetic levobupivacaine induces ferroptosis and inhibits progression by up-regulating p53 in non-small cell lung cancer. Aging (Albany NY). 2021;13. doi:10.18632/aging.203138.

70. Liu J, Li J, Kang R, Tang D. Cell type-specific induction of ferroptosis to boost antitumor immunity. Oncoimmunol. 2023;12 (1):2282252. doi:10.1080/2162402X.2023.2282252.

71. Demuynck R, Efimova I, Catanzaro E, Krysko DV. Ferroptosis: friend or foe in cancer immunotherapy? Oncoimmunol. 2023;12 (1):2182992. doi:10.1080/2162402X.2023.2182992.

72. Sprooten J, Laureano RS, Vanmeerbeek I, Govaerts J, Naulaerts S, Borras DM, Kinget L, Fucikova J, Spisek R, Jelinkova LP, et al. Trial watch: chemotherapy-induced immunogenic cell death in oncology. Oncoimmunol. 2023;12(1):2219591. doi:10.1080/2162402X.2023.2219591.

73. Gu JH, Liu CC, Xie JL, Ma B, Cui SM, Yang GZ, He SC. The Local Anesthetic Bupivacaine Inhibits the Progression of Non-Small Cell Lung Cancer by Inducing Autophagy Through Akt/mTOR Signaling. Front Oncol. 2021;11:616445. doi:10.3389/fonc.2021.616445.

74. Lirk P, Berger R, Hollmann MW, Fiegl H. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. British J Anaesthesia. 2012;109(2):200–207. doi:10.1093/bja/aes128.

75. Villar-Garea A, Fraga MF, Espada J, Esteller M. Procaine is a DNA-demethylating agent with growth-inhibitory effects in human cancer cells. Cancer Res. 2003;63:4984–4989.

76. Sabit H, Samy MB, Said OA, El-Zawahri MM. Procaine induces epigenetic changes in HCT116 colon cancer cells. Genetics Res Int. 2016;2016:8348450. doi:10.1155/2016/8348450.

77. Lirk P, Hollmann MW, Fleischer M, Weber NC, Fiegl H. Lidocaine and ropivacaine, but not bupivacaine, demethylate deoxyribonucleic acid in breast cancer cells in vitro. British J Anaesthesia. 2014;113 Suppl 1:i32–8. doi:10.1093/bja/aeu201.

78. Gao Z, Xu Z, Hung MS, Lin YC, Wang T, Gong M, Zhi X, Jablons DM, You L. Procaine and procainamide inhibit the Wnt canonical pathway by promoter demethylation of WIF-1 in lung cancer cells. Oncol Rep. 2009;22(6):1479–1484. doi:10.3892/or_00000590.

79. Qu X, Yang L, Shi Q, Wang X, Wang D, Wu G. Lidocaine inhibits proliferation and induces apoptosis in colorectal cancer cells by upregulating mir-520a-3p and targeting EGFR. Pathol Res Pract. 2018;214(12):1974–1979. doi:10.1016/j.prp.2018.09.012.

80. Xia W, Wang L, Yu D, Mu X, Zhou X. Lidocaine inhibits the progression of retinoblastoma in vitro and in vivo by modulating the miR–520a–3p/EGFR axis. Mol Med Rep. 2019;20(2):1333–1342. doi:10.3892/mmr.2019.10363.

81. Sui H, Lou A, Li Z, Yang J. Lidocaine inhibits growth, migration and invasion of gastric carcinoma cells by up-regulation of miR-145. BMC Cancer. 2019;19(1):233. doi:10.1186/s12885-019-5431-9.

82. 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 miR-520a-3p. Onco Targets Ther. 2020;13:5309–5321. doi:10.2147/OTT.S244550.

83. Wang Z, Liu Q, Lu J, Cao J, Wang XY, Chen Y. Lidocaine promotes autophagy of SH-SY5Y cells through inhibiting PI3K/AKT/mTOR pathway by upregulating miR-145. Toxicol Res. 2020;9(4):467–473. doi:10.1093/toxres/tfaa049.

84. Ju C, Zhou J, Miao H, Chen X, Zhang Q. Bupivacaine suppresses the progression of gastric cancer through regulating circ_0000376/miR-145-5p axis. BMC Anesthesiol. 2020;20(1):275. doi:10.1186/s12871-020-01179-4.

85. Lin CY, Tseng WT, Chang YY, Tsai MH, Chuang EY, Lu TP, Lai LC. Lidocaine and bupivacaine downregulate MYB and DANCR lncRNA by upregulating miR-187-5p in MCF-7 cells. Front Med (Lausanne). 2021;8:732817. doi:10.3389/fmed.2021.732817.

86. Zhu J, Han S. Lidocaine inhibits cervical cancer cell proliferation and induces cell apoptosis by modulating the lncRNA-MEG3/miR-421/BTG1 pathway. Am J Transl Res. 2019;11:5404–5416.

87. Zhao L, Ma N, Liu G, Mao N, Chen F, Li J. Lidocaineinhibits hepatocellular carcinoma development by modulating circ_ITCH/miR-421/CPEB3 axis. Dig Dis Sci. 2021;66(12):4384–4397. doi:10.1007/s10620-020-06787-1.

88. Guan E, Liu H, Xu N. Lidocaine suppresses gastric cancer development through circ_ANO5/miR-21-5p/LIFR axis. Dig Dis Sci. 2022;67(6):2244–2256. doi:10.1007/s10620-021-07055-6.

89. Wang H, Zhang X, Li Y, Li Y, Pang T. Lidocaine hampers colorectal cancer process via circITFG2/miR-1204/SOCS2 axis. Anticancer Drugs. 2022;33(3):235–244. doi:10.1097/CAD.0000000000001091.

90. Zi H, Chen L, Ruan Q. Lidocaine represses the malignant behavior of lung carcinoma cells via the circ_PDZD8/miR-516b-5p/GOLT1A axis. Histol Histopathol. 2022;37(5):461–474. doi:10.14670/HH-18-423.

91. Wen J, Li X, Ding Y, Zheng S, Xiao Y. Lidocaine inhibits glioma cell proliferation, migration and invasion by modulating the circEZH2/miR-181b-5p pathway. Neuroreport. 2021;32(1):52–60. doi:10.1097/WNR.0000000000001560.

92. Chen X, Liu W, Guo X, Huang S, Song X. Ropivacaine inhibits cervical cancer cell growth via suppression of the miR☐96/MEG2/pSTAT3 axis. Oncol Rep. 2020;43(5):1659–1668. doi:10.3892/or.2020.7521.

93. Liu R, Wu M, Xu G, Ju L, Xiao J, Zhong W, He X, Yang Y. Ropivacaine inhibits proliferation, migration, and invasion while inducing apoptosis of glioma cells by regulating the SNHG16/miR-424-5p axis. Open Life Sci. 2020;15(1):988–999. doi:10.1515/biol-2020-0108.

94. Lu Y, Yang C, Zhang L, Ding J. Ropivacaine retards the viability, migration, and invasion of choriocarcinoma cells by regulating the long noncoding RNA OGFRP1/MicroRNA-4731-5p/HIF3A axis. Mol Biotechnol. 2022;64(5):499–509. doi:10.1007/s12033-021-00429-1.

95. Deng Z, Jian Y, Cai H. Ropivacaine represses the proliferation, invasion, and migration of glioblastoma via modulating the microRNA-21-5p/KAT8 regulatory NSL complex subunit 2 axis. Bioengineered. 2022;13(3):5975–5986. doi:10.1080/21655979.2022.2037955.

96. Zhao L, Han S, Hou J, Shi W, Zhao Y, Chen Y. The local anesthetic ropivacaine suppresses progression of breast cancer by regulating miR-27b-3p/YAP axis. Aging (Albany NY). 2021;13(12):16341–16352. doi:10.18632/aging.203160.

97. Wang Y, Xie J, Liu W, Zhang R, Huang S, Xing Y. Lidocaine sensitizes the cytotoxicity of 5-fluorouacil in melanoma cells via upregulation of microRNA-493. Pharmazie. 2017;72(11):663–669. doi:10.1691/ph.2017.7616.

98. Liu T, Jiang F, Yu LY, Wu YY. Lidocaine represses proliferation and cisplatin resistance in cutaneous squamous cell carcinoma via miR-30c/SIRT1 regulation. Bioengineered. 2022;13(3):6359–6370. doi:10.1080/21655979.2022.2031419.

99. Yang Q, Zhang Z, Xu H, Ma C. Lidocaine alleviates cytotoxicity-resistance in lung cancer A549/DDP cells via down-regulation of miR-21. Mol Cell Biochem. 2019;456(1–2):63–72. doi:10.1007/s11010-018-3490-x.

100. Zhang X, Gu G, Li X, Zhang C. Lidocaine alleviates cisplatin resistance and inhibits migration of MGC-803/DDP cells through decreasing miR-10b. Cell Cycle. 2020;19(19):2530–2537. doi:10.1080/15384101.2020.1809914.

101. Cata JP, Ramirez MF, Velasquez JF, Di AI, Popat KU, Gottumukkala V, Black DM, Lewis VO, Vauthey JN. Lidocaine stimulates the function of natural killer cells in different experimental settings. Anticancer Res. 2017;37(9):4727–4732. doi:10.21873/anticanres.11879.

102. Ramirez MF, Tran P, Cata JP. The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. Reg Anesth Pain Med. 2015;40(1):43–48. doi:10.1097/AAP.0000000000000191.

103. Wei Q, Xia M, Zhang Q, Wang Z. Effect of intravenous lidocaine infusion on perioperative cellular immunity and the quality of postoperative recovery in breast cancer patients: a randomized controlled trial. Gland Surg. 2022;11(3):599–610. doi:10.21037/gs-22-134.

104. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. Anesth Analg. 2009;109(5):1464–1469. doi:10.1213/ANE.0b013e3181bab1bd.

105. Wang HL, Yan HD, Liu YY, Sun BZ, Huang R, Wang XS, Lei WF. Intraoperative intravenous lidocaine exerts a protective effect on cell-mediated immunity in patients undergoing radical hysterectomy. Mole Med Rep. 2015;12(5):7039–7044. doi:10.3892/mmr.2015.4235.

106. Dong H, Zhang Y, Xi H. The effects of epidural anaesthesia and analgesia on natural killer cell cytotoxicity and cytokine response in patients with epithelial ovarian cancer undergoing radical resection. J Int Med Res. 2012;40(5):1822–1829. doi:10.1177/030006051204000520.

107. 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):3089–3098. doi:10.3748/wjg.v18.i24.3089.

108. Zheng N, Wang T, Luo Q, Liu Y, Yang J, Zhou Y, Xie G, Ma Y, Yuan X, Shen L. M2 macrophage-derived exosomes suppress tumor intrinsic immunogenicity to confer immunotherapy resistance. Oncoimmunol. 2023;12(1):2210959. doi:10.1080/2162402X.2023.2210959.

109. Barnestein R, Galland L, Kalfeist L, Ghiringhelli F, Ladoire S, Limagne E. Immunosuppressive tumor microenvironment modulation by chemotherapies and targeted therapies to enhance immunotherapy effectiveness. Oncoimmunol. 2022;11(1):2120676. doi:10.1080/2162402X.2022.2120676.

110. Liu P, Chen J, Zhao L, Hollebecque A, Kepp O, Zitvogel L, Kroemer G. PD-1 blockade synergizes with oxaliplatin-based, but not cisplatin-based, chemotherapy of gastric cancer. Oncoimmunol. 2022;11(1):2093518. doi:10.1080/2162402X.2022.2093518.

111. Gong X, Dan J, Li F, Wang L. Suppression of mitochondrial respiration with local anesthetic ropivacaine targets breast cancer cells. Journal of Thoracic Disease. 2018;10(5):2804–2812. doi:10.21037/jtd.2018.05.21.

112. Karniel M, Beitner R. Local anesthetics induce a decrease in the levels of glucose 1, 6-bisphosphate, fructose 1,6-bisphosphate, and ATP, and in the viability of melanoma cells. J Thorac Dis. 2000;69(1):40–45. doi:10.1006/mgme.1999.2954.

113. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiol. 2001;94(6):1066–1073. doi:10.1097/00000542-200106000-00022.

114. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, Kavanagh BP, Buggy DJ. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer

surgery. Reg Anesth Pain Med. 2010;35(6):490–495. doi:10.1097/AAP.0b013e3181ef4d05.

115. Sultan SS. Paravertebral block can attenuate cytokine response when it replaces general anesthesia for cancer breast surgeries. Saudi J Anaesth. 2013;7(4):373–377. doi:10.4103/1658-354X.121043.

116. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, Wu CT. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. British J Anaesthes. 2006;97(5):640–646. doi:10.1093/bja/ael217.

117. Zhao T, Xia WH, Zheng MQ, Lu CQ, Han X, Sun YJ. Surgical excision promotes tumor growth and metastasis by promoting expression of MMP-9 and VEGF in a breast cancer model. Exper Oncol. 2008;30:60–64.

118. Kochhar A, Banday J, Ahmad Z, Panjiar P, Vajifdar H. Cervical epidural analgesia combined with general anesthesia for head and neck cancer surgery: a randomized study. J Anaesthesiol Clin Pharmacol. 2020;36(2):182–186. doi:10.4103/joacp.JOACP_72_19 .

119. O'Riain SC, Buggy DJ, Kerin MJ, Watson RWG, 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. Anesth Analg. 2005;100 (1):244–249. doi:10.1213/01.ANE.0000143336.37946.7D.

120. Piegeler T, Votta-Velis EG, Liu G, Place AT, Schwartz DE, Beck-Schimmer B, Minshall RD, Borgeat A. Antimetastatic potential of amide-linked local anesthetics: inhibition of lung adenocarcinoma cell migration and inflammatory Src signaling independent of sodium channel blockade. Anesthesiol. 2012;117(3):548–559. doi:10.1097/ALN.0b013e3182661977.

121. Chamaraux-Tran TN, Muller M, Pottecher J, Diemunsch PA, Tomasetto C, Namer IJ, Dali-Youcef N. Metabolomic Impact of Lidocaine on a Triple Negative Breast Cancer Cell Line. Front Pharmacol. 2022;13:821779. doi:10.3389/fphar.2022.821779.

122. Chen D, Yan Y, Xie J, Pan J, Chen Y, Li Q, Yuan Y, Zeng W, Xing W. Amide-type local anesthetics may suppress tumor cell proliferation and sensitize Human Hepatocellular Carcinoma Cells to Cisplatin via upregulation of RASSF1A expression and demethylation. J Cancer. 2020;11(24):7312–7319. doi:10.7150/jca.46630.

123. Zhang X, Pang W, Liu H, Wang J. Lidocine potentiates the cytotoxicity of 5-fluorouracil to choriocarcinoma cells by downregulating ABC transport proteins expression. J Cell Biochem. 2019;120 (10):16533–16542. doi:10.1002/jcb.28913.

124. Li K, Yang J, Han X. Lidocaine sensitizes the cytotoxicity of cisplatin in breast cancer cells via up-regulation of RARbeta2 and RASSF1A demethylation. Int J Mol Sci. 2014;15(12):23519–23536. doi:10.3390/ijms151223519.

125. Freeman J, Crowley PD, Foley AG, Gallagher HC, Iwasaki M, Ma D, Buggy DJ. Effect of perioperative lidocaine and cisplatin on metastasis in a murine model of breast cancer surgery. Anticancer Res. 2018;38(10):5599–5606. doi:10.21873/anticanres.12894.

126. Viale M, Vannozzi MO, Mandys V, Esposito M. Time-dependent influence of procaine hydrochloride on cisplatin antitumor activity in P388 tumor bearing mice. Anticancer Res. 2001;21:485–487.

127. Yang X, Zhao L, Li M, Yan L, Zhang S, Mi Z, Ren L, Xu J. Lidocaine enhances the effects of chemotherapeutic drugs against bladder cancer. Sci Rep. 2018;8(1):598. doi:10.1038/s41598-017-19026-x.

128. Zeng W, Xing ZT, Tan MY, Wu YW, Zhang CY. Lidocaine suppresses the malignant behavior of gastric cancer cells via the c-Met/c-Src pathway. Exp Ther Med. 2021;21(5):424. doi:10.3892/etm.2021.9868.

129. Bezu L, Kepp O, Kroemer G. Local anesthetics and immunotherapy: a novel combination to fight cancer. Semin Immunopathol. 2023;45(2):265–272. doi:10.1007/s00281-022-00960-6.

130. Tang X, Li M, Wu X, Guo T, Zhang L, Tang L, Jia F, Hu Y, Zhang Y, Xing X, et al. Neoadjuvant PD-1 blockade plus chemotherapy induces a high pathological complete response rate and anti-tumor immune subsets in clinical stage III gastric cancer. Oncoimmunol. 2022;11(1):2135819. doi:10.1080/2162402X.2022.2135819.

131. Song M, Huang Y, Hong Y, Liu J, Zhu J, Lu S, Wang J, Sun F, Huang J, Xu J, et al. PD-L1-expressing natural killer cells predict favorable prognosis and response to PD-1/PD-L1 blockade in neuroblastoma. Oncoimmunol. 2024;13(1):2289738. doi:10.1080/2162402X.2023.2289738.

132. Russo M, Panini N, Fabbrizio P, Formenti L, Becchetti R, Matteo C, Meroni M, Nastasi C, Cappelleri A, Frapolli R, et al. Chemotherapy-induced neutropenia elicits metastasis formation in mice by promoting proliferation of disseminated tumor cells. Oncoimmunol. 2023;12(1):2239035. doi:10.1080/2162402X.2023.2239035.

133. Han BS, Jung KH, Lee JE, Yoon YC, Ko S, Park MS, Lee YJ, Kim SE, Cho YJ, Lee P, et al. Lidocaine enhances the efficacy of palbociclib in triple-negative breast cancer. Am J Cancer Res. 2022;12 (7):3083–3098.

134. Holler JP, Ahlbrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, Hecker A, Padberg W, Weigand MA. Peridural 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):989–993. doi:10.1097/SLA.0b013e3182915f61.

135. 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 Anaesth. 2011;106(6):814–822. doi:10.1093/bja/aer055.

136. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, Chen W, Miao C. Association between intraoperative intravenous lidocaine infusion and survival in patients undergoing pancreatectomy for pancreatic cancer: a retrospective study. Br J Anaesth. 2020;125(2):141–148. doi:10.1016/j.bja.2020.03.034.

137. Wang X, Xie W, Gan S, Wang T, Chen X, Su D, Sun J, Lin J, Wu F, Xu P, et al. Effects of general anesthesia versus local anesthesia in primary hepatocellular carcinoma patients presenting for thermal ablation surgery: a multiple center retrospective cohort study with propensity score matching. Ann Transl Med. 2020;8(6):277. doi:10.21037/atm.2020.03.88.

138. 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 colectomy: a population-based study. Anesthesiol. 2012;116(4):797–806. doi:10.1097/ALN.0b013e31824674f6.

139. Zimmitti G, Soliz J, Aloia TA, Gottumukkala V, Cata JP, Tzeng CW, Vauthey JN. Positive impact of epidural analgesia on oncologic outcomes in patients undergoing resection of colorectal liver metastases. Ann Surg Oncol. 2016;23(3):1003–1011. doi:10.1245/s10434-015-4933-1.

140. Hiller JG, Hacking MB, Link EK, Wessels KL, Riedel BJ. Perioperative epidural analgesia reduces cancer recurrence after gastro-oesophageal surgery. Acta Anaesthesiol Scand. 2014;58 (3):281–290. doi:10.1111/aas.12255.

141. Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, Durieux ME, Nemergut EC. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anesthesiol. 2010;113(1):27–34. doi:10.1097/ALN.0b013e3181de6d0d.

142. Gupta A, Bjornsson A, Fredriksson M, Hallbook O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. Br J Anaesth. 2011;107(2):164–170. doi:10.1093/bja/aer100.

143. Merquiol F, Montelimard AS, Nourissat A, Molliex S, Zufferey PJ. Cervical epidural anesthesia is associated with increased cancer-free survival in laryngeal and hypopharyngeal cancer surgery: a retrospective propensity-matched analysis. Regional Anesthesia and Pain Medicine. 2013;38(5):398–402. doi:10.1097/AAP.0b013e31829cc3fb.

144. Wuethrich PY, Hsu Schmitz SF, Kessler TM, Thalmann GN, Studer UE, Stueber F, Burkhard FC. Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study.

Anesthesiol. 2010;113(3):570–576. doi:10.1097/ALN.0b013e3181e4f6ec.

145. Gao H, Meng XY, Wang HQ, Zhu FF, Guo AL, Zhu M, Song JC, Yu WF. Association between anaesthetic technique and oncological outcomes after colorectal carcinoma liver metastasis resection. Int. J. Med. Sci. 2019;16(2):337–342. doi:10.7150/ijms.28016.

146. Cazenave L, Faucher M, Tourret M, Marques M, Tezier M, Mokart D. Intravenous lidocaine and cancer outcomes after radical cystectomy. Eur. J. Anaesthesiol. 2022;39(4):396–399. doi:10.1097/EJA.0000000000001559.

147. Zhang H, Gu J, Qu M, Sun Z, Huang Q, Cata JP, Chen W, Miao C. Effects of intravenous infusion of lidocaine on short-term outcomes and survival in patients undergoing surgery for ovarian cancer: a retrospective propensity score matching study. Front Oncol. 2021;11:689832. doi:10.3389/fonc.2021.689832.

148. Cummings Iii KC, Kou TD, Chak A, Schluchter MD, Margevicius S, Cooper GS, Meropol NJ, Perry Y, Linden PA, Cummings LC. Surgical approach and the impact of epidural analgesia on survival after esophagectomy for cancer: a population-based retrospective cohort study. PLoS One. 2019;14(1):e0211125. doi:10.1371/journal.pone.0211125.

149. Li W, Li Y, Huang Q, Ye S, Rong T. Short and long-term outcomes of epidural or intravenous analgesia after esophagectomy: a propensity-matched cohort study. PLoS One. 2016;11(4):e0154380. doi:10.1371/journal.pone.0154380.

150. Wang J, Guo W, Wu Q, Zhang R, Fang J. Impact of combination epidural and general anesthesia on the long-term survival of gastric cancer patients: a retrospective study. Med Sci Monit. 2016;22:2379–2385. doi:10.12659/msm.899543.

151. de Oliveira Gs AS Jr., Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ, McCarthy RJ. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. Reg Anesth Pain Med. 2011;36(3):271–277. doi:10.1097/AAP.0b013e318217aada.

152. Elias KM, Kang S, Liu X, Horowitz NS, Berkowitz RS, Frendl G. Anesthetic selection and disease-free survival following optimal primary cytoreductive surgery for stage III epithelial ovarian cancer. Ann. Surg. Oncol. 2015;22(4):1341–1348. doi:10.1245/s10434-014-4112-9.

153. Tseng JH, Cowan RA, Afonso AM, Zhou Q, Iasonos A, Ali N, Thompson E, Sonoda Y, O'Cearbhaill RE, Chi DS, et al. Perioperative epidural use and survival outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer. Gynecol Oncol. 2018;151(2):287–293. doi:10.1016/j.ygyno.2018.08.024.

154. Chen W, Xu Y, Zhang Y, Lou W, Han X. Positive impact of intraoperative epidural ropivacaine infusion on oncologic outcomes in pancreatic cancer patients undergoing pancreatectomy: a retrospective cohort study. J Cancer. 2021;12(15):4513–4521. doi:10.7150/jca.57661.

155. Chipollini J, Alford B, Boulware DC, Forget P, Gilbert SM, Lockhart JL, Pow-Sang JM, Sexton WJ, Spiess PE, Poch MA, et al. Epidural anesthesia and cancer outcomes in bladder cancer patients: is it the technique or the medication? A matched-cohort analysis from a tertiary referral center. BMC Anesthesiol. 2018;18(1):157. doi:10.1186/s12871-018-0622-5.

156. Cao L, Chang Y, Lin W, Zhou J, Tan H, Yuan Y, Zeng W. Long-term survival after resection of hepatocelluar carcinoma: a potential risk associated with the choice of postoperative analgesia. Anesth Analg. 2014;118(6):1309–1316. doi:10.1213/ANE.0000000000000207.

157. Binczak M, Tournay E, Billard V, Rey A, Jayr C. Major abdominal surgery for cancer: does epidural analgesia have a long-term effect on recurrence-free and overall survival? Ann Fr Anesth Reanim. 2013;32(5):e81–8. doi:10.1016/j.annfar.2013.02.027.

158. Christopher Doiron R, Jaeger M, Booth CM, Wei X, Robert Siemens D. Is there a measurable association of epidural use at cystectomy and postoperative outcomes? a population-based study. Can Urol Assoc J. 2016;10(9–10):321–327. doi:10.5489/cuaj.3856.

159. Cata JP, Chavez-MacGregor M, Valero V, Black W, Black DM, Goravanchi F, Ifeanyi IC, Hernandez M, Rodriguez-Restrepo A, Gottumukkala V. The impact of paravertebral block analgesia on breast cancer survival after surgery. Reg Anesth Pain Med. 2016;41(6):696–703. doi:10.1097/AAP.0000000000000479.

160. 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 Anaesth. 2010;105(2):145–149. doi:10.1093/bja/aeq156 .

161. Wurster EF, Pianka F, Warschkow R, Antony P, Brenner T, Weigand MA, Schmied BM, Buchler MW, Tarantino I, Ulrich A. Peridural analgesia does not impact survival in patients after colon cancer resection: a retrospective propensity score-adjusted analysis. Int. J. Colorectal Dis. 2019;34(7):1283–1293. doi:10.1007/s00384-019-03315-0.

162. Wu HL, Tai YH, Mandell MS, Tsou MY, Yang SH, Chen TH, Chang KY. Effect of epidural analgesia on cancer prognosis after colon cancer resection: a single-centre cohort study in Taiwan. BMJ open. 2020;10(10):e036577. doi:10.1136/bmjopen-2019-036577.

163. Hasselager RP, Hallas J, Gogenur I. Epidural analgesia and recurrence after colorectal cancer surgery: a danish retrospective registry-based cohort study. Anesthesiol. 2022;136(3):459–471. doi:10.1097/ALN.0000000000004132.

164. Day A, Smith R, Jourdan I, Fawcett W, Scott M, Rockall T. Retrospective analysis of the effect of postoperative analgesia on survival in patients after laparoscopic resection of colorectal cancer. Br J Anaesth. 2012;109(2):185–190. doi:10.1093/bja/aes106.

165. Tai YH, Chang WK, Wu HL, Chan MY, Chen HH, Chang KY, Ahmad A. The effect of epidural analgesia on cancer progression in patients with stage IV colorectal cancer after primary tumor resection: a retrospective cohort study. PloS one. 2018;13(7):e0200893. doi:10.1371/journal.pone.0200893.

166. Heinrich S, Janitz K, Merkel S, Klein P, Schmidt J. Short- and long term effects of epidural analgesia on morbidity and mortality of esophageal cancer surgery. Langenbeck's Arch. Surg. 2015;400(1):19–26. doi:10.1007/s00423-014-1248-9.

167. Cummings KC 3rd, Patel M, Htoo PT, Bakaki PM, Cummings LC, Koroukian S. A comparison of the effects of epidural analgesia versus traditional pain management on outcomes after gastric cancer resection: a population-based study. Reg Anesth Pain Med. 2014;39(3):200–207. doi:10.1097/AAP.0000000000000079.

168. Pei JP, Zhang CD, Liang Y, Zhang C, Wu KZ, Zhao ZM, Dai DQ. Effects of epidural combined with general anesthesia versus general anesthesia alone in gastric cancer surgery: a propensity score matching analysis. Ann Transl Med. 2020;8(7):473. doi:10.21037/atm.2020.03.127.

169. Chang WK, Lee MY, Tai YH, Kuo YM, Tsou MY, Chang KY. Does epidural analgesia improve the cancer outcome in hepatocellular carcinoma after resection surgery? A retrospective analysis. J Chin Med Assoc. 2019;82(4):295–299. doi:10.1097/JCMA.0000000000000054.

170. Cata JP, Gottumukkala V, Thakar D, Keerty D, Gebhardt R, Liu DD. Effects of postoperative epidural analgesia on recurrence-free and overall survival in patients with nonsmall cell lung cancer. J Clin Anesth. 2014;26(1):3–17. doi:10.1016/j.jclinane.2013.06.007.

171. Wu HL, Tai YH, Chan MY, Tsou MY, Chen HH, Chang KY. Effects of epidural analgesia on cancer recurrence and long-term mortality in patients after non-small-cell lung cancer resection: a propensity score-matched study. BMJ open. 2019;9(5):e027618. doi:10.1136/bmjopen-2018-027618.

172. 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 Anaesth. 2012;109(2):253–259. doi:10.1093/bja/aes176.

173. Lacassie HJ, Cartagena J, Branes J, Assel M, Echevarria GC. The relationship between neuraxial anesthesia and advanced ovarian

cancer-related outcomes in the Chilean population. Anesth Analg. 2013;117(3):653–660. doi:10.1213/ANE.0b013e3182a07046.

174. Capmas P, Billard V, Gouy S, Lhomme C, Pautier P, Morice P, Uzan C. Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. Anticancer Res. 2012;32:1537–1542.

175. Lin KJ, Hsu FK, Shyr YM, Ni YW, Tsou MY, Chang KY. Effect of epidural analgesia on long-term outcomes after curative surgery for pancreatic cancer: a single-center cohort study in Taiwan. J Chin Med Assoc. 2022;85(1):124–128. doi:10.1097/JCMA.0000000000000615.

176. Alexander A, Lehwald-Tywuschik N, Rehders A, Rabenalt S, Verde PE, Eisenberger CF, Picker N, Knoefel WT, Kienbaum P. Peridural Anesthesia and Cancer-Related Survival after Surgery for Pancreatic Cancer-A Retrospective Cohort Study. Clin pract. 2021;11(3):532–542. doi:10.3390/clinpract11030070.

177. Wuethrich PY, Thalmann GN, Studer UE, Burkhard FC. Epidural analgesia during open radical prostatectomy does not improve long-term cancer-related outcome: a retrospective study in patients with advanced prostate cancer. PloS one. 2013;8(8):e72873. doi:10.1371/journal.pone.0072873.

178. Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, Van Cangh P, Cosyns JP, De Kock M. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol. 2011;28(12):830–835. doi:10.1097/EJA.0b013e32834b7d9a.

179. Tsui BC, Rashiq S, Schopflocher D, Murtha A, Broemling S, Pillay J, Finucane BT. Epidural anesthesia and cancer recurrence rates after radical prostatectomy. Can J Anaesth. 2010;57(2):107–112. doi:10.1007/s12630-009-9214-7.

180. Wu HL, Tai YH, Lin SP, Yang SH, Tsou MY, Chang KY. Epidural analgesia does not impact recurrence or mortality in patients after rectal cancer resection. Sci Rep. 2021;11(1):913. doi:10.1038/s41598-020-79657-5.

181. Shin S, Kim HI, Kim NY, Lee KY, Kim DW, Yoo YC. Effect of postoperative analgesia technique on the prognosis of gastric cancer: a retrospective analysis. Oncotarget. 2017;8(61):104594–104604. doi:10.18632/oncotarget.21979.

182. Chen WK, Miao CH, Landoni G. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. PloS one. 2013;8(2):e56540. doi:10.1371/journal.pone.0056540.

183. Pei L, Tan G, Wang L, Guo W, Xiao B, Gao X, Wang L, Li H, Xu Z, Zhang X, et al. Comparison of combined general-epidural anesthesia with general anesthesia effects on survival and cancer recurrence: a meta-analysis of retrospective and prospective studies. PloS one. 2014;9(12):e114667. doi:10.1371/journal.pone.0114667.

184. Sun Y, Li T, Gan TJ. The effects of perioperative regional anesthesia and analgesia on cancer recurrence and survival after oncology surgery: a systematic review and meta-analysis. Reg Anesth Pain Med. 2015;40(5):589–598. doi:10.1097/AAP.0000000000000273.

185. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. Oncotarget. 2016;7(12):15262–15273. doi:10.18632/oncotarget.7683.

186. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI, Investigators ATG. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ. 2011;342(mar29 2):d1491. doi:10.1136/bmj.d1491 .

187. Karmakar MK, Samy W, Lee A, Li JW, Chan WC, Chen PP, Tsui BCH. 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):5813–5820. doi:10.21873/anticanres.12024.

188. Finn DM, Ilfeld BM, Unkart JT, Madison SJ, Suresh PJ, Sandhu NPS, Kormylo NJ, Malhotra N, Loland VJ, Wallace MS, et al. Post-mastectomy cancer recurrence with and without a continuous paravertebral block in the immediate postoperative period: a prospective multi-year follow-up pilot study of a randomized, triple-masked, placebo-controlled investigation. Journal of Anesthesia. 2017;31(3):374–379. doi:10.1007/s00540-017-2345-z.

189. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet. 2019;394(10211):1807–1815. doi:10.1016/S0140-6736(19)32313-X.

190. MacFater WS, Xia W, Barazanchi AWH, MacFater HS, Lightfoot N, Svirskis D, Kahokehr AA, Hill AG. Association between perioperative intraperitoneal local anaesthetic infusion and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial. ANZ J Surg. 2020;90(5):802–806. doi:10.1111/ans.15753.

191. Kim SY, Kim NK, Baik SH, Min BS, Hur H, Lee J, Noh HY, Lee JH, Koo BN. Effects of postoperative pain management on immune function after laparoscopic resection of colorectal cancer: a randomized study. Med. 2016;95(19):e3602. doi:10.1097/MD.0000000000003602.

192. Falk W, Magnuson A, Eintrei C, Henningsson R, Myrelid P, Matthiessen P, Gupta A. Comparison between epidural and intravenous analgesia effects on disease-free survival after colorectal cancer surgery: a randomised multicentre controlled trial. Br J Anaesth. 2021;127(1):65–74. doi:10.1016/j.bja.2021.04.002.

193. Xu D, Luo W. Effect of ropivacaine combined with small doses of triamcinolone and continuous nerve block of unilateral paravertebral canal guided by ultrasound on metastasis after radical treatment of lung cancer. J Oncol. 2022;2022:6310081. doi:10.1155/2022/6310081.

194. Xu ZZ, Li HJ, Li MH, Huang SM, Li X, Liu QH, Li J, Li XY, Wang DX, Sessler DI. Epidural anesthesia-analgesia and recurrence-free survival after lung cancer surgery: a randomized trial. Anesthesiol. 2021;135(3):419–432. doi:10.1097/ALN.0000000000003873.

195. Zhang H, Qu M, Guo K, Wang Y, Gu J, Wu H, Zhu X, Sun Z, Cata JP, Chen W, et al. Intraoperative lidocaine infusion in patients undergoing pancreatectomy for pancreatic cancer: a mechanistic, multicentre randomised clinical trial. Br J Anaesth. 2022;129(2):244–253. doi:10.1016/j.bja.2022.03.031.

196. Du YT, Li YW, Zhao BJ, Guo XY, Feng Y, Zuo MZ, Fu C, Zhou WJ, Li HJ, Liu YF, et al. Long-term survival after combined epidural-general anesthesia or general anesthesia alone: follow-up of a randomized trial. Anesthesiol. 2021;135(2):233–245. doi:10.1097/ALN.0000000000003835.

197. Ostovic H, Simac B, Prazetina M, Bradic N, Persec J. The effect of intravenous lidocaine, ketamine, and lidocaine-ketamine combination in colorectal cancer surgery: a randomized controlled trial. Anesth Analg. 2023. doi:10.1213/ANE.0000000000006555.

198. Guerrero Orriach JL, Raigon Ponferrada A, Malo Manso A, Herrera Imbroda B, Escalona Belmonte JJ, Ramirez Aliaga M, Ramirez Fernandez A, Diaz Crespo J, Soriano Perez AM, Fontaneda Heredia A, et al. Anesthesia in combination with propofol increases disease-free survival in bladder cancer patients who undergo radical tumor cystectomy as compared to inhalational anesthetics and opiate-based analgesia. Oncology. 2020;98(3):161–167. doi:10.1159/000504807.

199. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. Anesth Analg. 2008;107(1):325–332. doi:10.1213/ane.0b013e3181770f55.

200. Alexa AL, Ciocan A, Zaharie F, Valean D, Sargarovschi S, Breazu C, Al Hajjar N, Ionescu D. The Influence of Intravenous Lidocaine Infusion on Postoperative Outcome and Neutrophil-to-Lymphocyte Ratio in Colorectal Cancer Patients. A Pilot Study. J. Gastrointest. Liver Dis. 2023;32(2):156–161. doi:10.15403/jgld-4962.

201. Wu YF, Li XP, Yu YB, Chen L, Jiang CB, Li DY, Chen ML. Postoperative local incision analgesia for acute pain treatment in patients with hepatocellular carcinoma. Rev. Assoc. Med. Bras. 2018;64(2):175–180. doi:10.1590/1806-9282.64.02.175.

202. Hayden JM, Oras J, Block L, Thorn SE, Palmqvist C, Salehi S, Nordstrom JL, Gupta A. Intraperitoneal ropivacaine reduces time

interval to initiation of chemotherapy after surgery for advanced ovarian cancer: randomised controlled double-blind pilot study. Br J Anaesth. 2020;124(5):562–570. doi:10.1016/j.bja.2020.01.026.

203. Badwe RA, Parmar V, Nair N, Joshi S, Hawaldar R, Pawar S, Kadayaprath G, Borthakur BB, Rao Thammineedi S, Pandya S, et al. Effect of peritumoral infiltration of local anesthetic before surgery on survival in early breast cancer. J Clin Oncol. 2023;41 (18):3318–3328. doi:10.1200/JCO.22.01966.

204. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function in vitro. Br J Anaesth. 2009;103(5):685–690. doi:10.1093/bja/aep261.

205. Vanni G, Materazzo M, Perretta T, Meucci R, Anemona L, Buonomo C, Dauri M, Granai AV, Rho M, Ingallinella S, et al. Impact of awake breast cancer surgery on postoperative lymphocyte responses. vivo. 2019;33(6):1879–1884. doi:10.21873/invivo.11681.

206. Xu YJ, Chen WK, Zhu Y, Wang SL, Miao CH. Effect of thoracic epidural anaesthesia on serum vascular endothelial growth factor C and cytokines in patients undergoing anaesthesia and surgery for colon cancer. Br J Anaesth. 2014;113 Suppl 1:i49–55. doi:10.1093/bja/aeu148.

207. Wang L, Liang S, Chen H, Xu Y, Wang Y. The effects of epidural anaesthesia and analgesia on T lymphocytes differentiation markers and cytokines in patients after gastric cancer resection. BMC Anesthesiol. 2019;19(1):102. doi:10.1186/s12871-019-0778-7.

208. Sen Y, Xiyang H, Yu H. Effect of thoracic paraspinal block-propofol intravenous general anesthesia on VEGF and TGF-beta in patients receiving radical resection of lung cancer. Med. 2019;98 (47):e18088. doi:10.1097/MD.0000000000018088.

209. Hayden J, Gupta A, Thorn SE, Thulin P, Block L, Oras J. Does intraperitoneal ropivacaine reduce postoperative inflammation? A prospective, double-blind, placebo-controlled pilot study. Acta anaesthesiologica Scandinavica. 2019;63(8):1048–1054. doi:10.1111/aas.13410.

210. Huang XY, Wang HC, Yuan Z, Huang J, Zheng Q. Norepinephrine stimulates pancreatic cancer cell proliferation, migration and invasion via beta-adrenergic receptor-dependent activation of P38/MAPK pathway. Hepato-gastroenterology. 2012;59(115):889–893. doi:10.5754/hge11476.

211. Masur K, Niggemann B, Zanker KS, Entschladen F. Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers. Cancer Res. 2001;61:2866–2869.

212. Strell C, Niggemann B, Voss MJ, Powe DG, Zanker KS, Entschladen F. Norepinephrine promotes the beta1-integrin-mediated adhesion of MDA-MB-231 cells to vascular endothelium by the induction of a GROalpha release. Mol Cancer Res. 2012;10(2):197–207. doi:10.1158/1541-7786.MCR-11-0130.

213. An J, Feng L, Ren J, Li Y, Li G, Liu C, Yao Y, Yao Y, Jiang Z, Gao Y, et al. Chronic stress promotes breast carcinoma metastasis by accumulating myeloid-derived suppressor cells through activating beta-adrenergic signaling. Oncoimmunol. 2021;10(1):2004659. doi:10.1080/2162402X.2021.2004659.

214. Bezu L, Kepp O, Kroemer G. Immunogenic stress induced by local anesthetics injected into neoplastic lesions. Oncoimmunol. 2022;11 (1):2077897. doi:10.1080/2162402X.2022.2077897.

215. Kudling TV, Clubb JHA, Quixabeira DCA, Santos JM, Havunen R, Kononov A, Heinio C, Cervera-Carrascon V, Pakola S, Basnet S, et al. Local delivery of interleukin 7 with an oncolytic adenovirus activates tumor-infiltrating lymphocytes and causes tumor regression. Oncoimmunol. 2022;11(1):2096572. doi:10.1080/2162402X.2022.2096572.

216. Quixabeira DCA, Cervera-Carrascon V, Santos JM, Clubb JHA, Kudling TV, Basnet S, Heinio C, Gronberg-Vaha-Koskela S, Anttila M, Havunen R, et al. Local therapy with an engineered oncolytic adenovirus enables antitumor response in non-injected melanoma tumors in mice treated with aPD-1. Oncoimmunol. 2022;11(1):2028960. doi:10.1080/2162402X.2022.2028960.

217. Jin C, Ali A, Iskantar A, Fotaki G, Wang H, Essand M, Karlsson-Parra A, Yu D. Intratumoral administration of pro-inflammatory allogeneic dendritic cells improved the anti-tumor response of systemic anti-CTLA-4 treatment via unleashing a T cell-dependent response. Oncoimmunol. 2022;11(1):2099642. doi:10.1080/2162402X.2022.2099642.

218. Tang Y, Zhou C, Li Q, Cheng X, Huang T, Li F, He L, Zhang B, Tu S. Targeting depletion of myeloid-derived suppressor cells potentiates PD-L1 blockade efficacy in gastric and colon cancers. Oncoimmunol. 2022;11(1):2131084. doi:10.1080/2162402X.2022.2131084.

219. Brownlie D, von Kries A, Valenzano G, Wild N, Yilmaz E, Safholm J, Al-Ameri M, Alici E, Ljunggren HG, Schliemann I, et al. Accumulation of tissue-resident natural killer cells, innate lymphoid cells, and CD8(+) T cells towards the center of human lung tumors. Oncoimmunol. 2023;12(1):2233402. doi:10.1080/2162402X.2023.2233402.

220. Hassel JC, Schank TE, Smetak H, Muhlbauer J, Salzmann M, Machiraju D, Menzer C, Lang K, Konig L, Haefner MF, et al. Evaluation of radio-immunotherapy sequence on immunological responses and clinical outcomes in patients with melanoma brain metastases (ELEKTRA). Oncoimmunol. 2022;11(1):2066609. doi:10.1080/2162402X.2022.2066609.

221. Zeng Q, Yang J, Ji J, Wang P, Zhang L, Yan G, Wu Y, Chen Q, Liu J, Zhang G, et al. PD-L1 blockade potentiates the antitumor effects of ALA-PDT and optimizes the tumor microenvironment in cutaneous squamous cell carcinoma. Oncoimmunol. 2022;11 (1):2061396. doi:10.1080/2162402X.2022.2061396.

222. Steenbrugge J, Bellemans J, Vander Elst N, Demeyere K, De Vliegher J, Perera T, De Wever O, Van Den Broeck W, De Spiegelaere W, Sanders NN, et al. One cisplatin dose provides durable stimulation of anti-tumor immunity and alleviates anti-PD-1 resistance in an intraductal model for triple-negative breast cancer. Oncoimmunol. 2022;11(1):2103277. doi:10.1080/2162402X.2022.2103277.

223. Sun N, Gong J, Zhang W, Yang X, Liu J. Sevoflurane suppresses hepatocellular carcinoma cell progression via circ_0001649/miR-19a-3p/SGTB axis. Histol Histopathol. 2023;38(5):537–547. doi:10.14670/HH-18-484.

224. Zhu X, Peng C, Peng Z, Chang R, Guo Q. Sevoflurane inhibits metastasis in hepatocellular carcinoma by inhibiting MiR-665-induced activation of the ERK/MMP pathway. Cell Transplant. 2022;31:9636897221104447. doi:10.1177/09636897221104447.

225. Kang X, Li X, Li Y. Sevoflurane suppresses the proliferation, migration and invasion of colorectal cancer through regulating circ_0000423/miR-525-5p/SGPP1 network. Cell Mol Bioeng. 2022;15(2):219–230. doi:10.1007/s12195-021-00717-5.

226. Reid P, Sandigursky S, Song J, Lopez-Olivo MA, Safa H, Cytryn S, Efuni E, Buni M, Pavlick A, Krogsgaard M, et al. Safety and effectiveness of combination versus monotherapy with immune checkpoint inhibitors in patients with preexisting autoimmune diseases. Oncoimmunol. 2023;12(1):2261264. doi:10.1080/2162402X.2023.2261264.