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Lidocaine as a Potential Anti-Cancer Drug

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ABSTRACT

Lidocaine, a widely used local anesthetic, has shown potential for drug repositioning in oncology due to its multi-targeted biological effects. There is evidence that lidocaine inhibits cancer cell proliferation, induces apoptosis, and suppresses metastasis through mechanisms including PI3K/AKT/mTOR pathway inhibition and voltage-gated sodium channel blockade. It also modulates the tumor microenvironment by reducing inflammatory signaling and cytokine release. Additionally, lidocaine demonstrates promise as a chemosensitizer by enhancing the efficacy of anti-cancer agents such as cisplatin and 5-fluorouracil, partly through inhibition of drug efflux transporters and epigenetic reactivation of tumor suppressor genes. This review analyzes current evidence on lidocaine as a potential anti-cancer drug and evaluates its efficacy and future potential. While preclinical findings are encouraging, clinical translation remains limited due to uncertainties in dosage, pharmacokinetics, and tumor heterogeneity. Further research is required to define its therapeutic role as an adjunct in cancer treatment.

Keywords
Anti-cancer compounds, Therapy, Lidocaine

Abbreviations
ATP-binding cassette- ABC, ATP-binding cassette sub-family B member 1- ABCB1, BCL2 Associated X, Apoptosis Regulator- Bax, Breast cancer resistance protein- BCRP, B-cell lymphoma 2- Bcl-2, Colorectal cancer- CRC, Extracellular matrix- ECM, Extracellular Signal-Regulated Kinases 1 and 2-ERK1/2, High mobility group box 1- HMGB1, Interleukin-6- IL-6, Intravenous- IV, Mechanistic Target of Rapamycin- mTOR, Metalloproteinase- MMP, Mitogen-activated protein kinases- MAPK, Mitomycin C- MMC, Multi-drug resistance- MDR, Multi-drug resistance associated protein 1- MRP1, Nuclear factor kappa-B- NF-kB, Natural killer- NK, Phosphoinositide 3-kinase- PI3K, Protein kinase B- PKB, AKT, P-glycoprotein- P-gp, Ras association domain family 1 isoform A- RASSF1A, Retinoic Acid Receptor beta 2- RARβ2, Sodium-Hydrogen Antiporter 1- NHE1, Subcutaneous- SC, Toll-like receptors- TLR, Tumor necrosis factor alpha- TNF-α, Voltage-gated sodium channel- VGSC, 5-fluorouracil- 5-FU.

Introduction
Lidocaine is a widely utilized local anesthetic that is classified as a tertiary amide and a class Ib anti-arrhythmic agent. It displays a range of physiological effects including anti-nociceptive, anti-arrhythmic, anti-inflammatory, and anti-thrombotic properties. Its primary mechanism of action involves the reversible blockage of voltage-gated sodium channels (VGSC), thereby inhibiting the propagation of action potentials along neuronal membranes. In addition to this pathway, lidocaine has been shown to modulate multiple others including nicotinic and acetylcholine receptors, muscarinic cholinergic receptors, presynaptic calcium channels in dorsal root ganglia, and opioid receptors [1]. It also influences neurite growth and interferes with substance P binding to natural killer (NK) cell receptors [2,3].

Beyond neuronal signaling, lidocaine exerts effects on key inflammatory and immune-related pathways. These include the modulation of toll-like receptors (TLR), inhibition of nuclear factor kappa-B (NF-kB) signaling, and downstream suppression of cytokine effectors such as high mobility group box 1 (HMGB1)

and tumor necrosis factor-α (TNF-α). Collectively these mechanisms contribute to lidocaine's well-established clinical outcome of localized analgesia, or loss of sensation or numbing of the affected area [4]. These pathways are also critically involved in tumor progression as chronic inflammation contributes to tumor growth, angiogenesis, and immune evasion [5]. With lidocaine's ability to modulate inflammation through multiple facets, it could potentially create an anti-tumor microenvironment.

Clinically, lidocaine is most used in dentistry, minor surgical procedures, and topically to provide patients with short-term pain relief [6]. Additionally, it is frequently combined with epinephrine (adrenaline) to prolong anesthetic duration and induce vasoconstriction, reducing intraoperative bleeding [7]. Lidocaine can be administered via multiple routes, including through intravenous (IV) and subcutaneous (SC) injections, and topically as a cream or gel [8]. This multi-modality makes it highly versatile in pre-hospital, perioperative, and postoperative settings.

The pharmacological diversity of lidocaine remains unquestioned by its wide range of uses. This has prompted a growing interest in repositioning it for potential avenues of novel applications. Drug repositioning refers to pre-existing drugs that are reallocated to new disease treatment. The cost-effective and time-efficient advantages of this has pushed the notion of lidocaine as an anti-cancer drug. In this instance, lidocaine gained traction in the oncologic realm due to the growing body of evidence that various cancer cell lines exhibit suppressed cell growth, proliferation, and metastasis, as well as direct cell death (apoptosis) following exposure to lidocaine during oncologic surgical procedures [9].

A major challenge in cancer therapy is the development of multi-drug resistance (MDR) through varying mechanisms, which significantly limits the efficacy of conventional chemotherapeutics. Cancer cells can overexpress ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp/ABCB1), MRP1, and BCRP, which in turn actively pump chemotherapeutic agents out of the cell [10]. This pumping allows the cancer cell to expel anti-cancer drugs more efficiently, resulting in survival advantages. Additionally, enhanced DNA repair of platinum-drug-treated strands, metabolic alterations that either reduce uptake or accelerate metabolism of chemotherapeutics, and evasion of apoptosis (e.g., activating PI3K/AKT) are all ways that cancerous cells have evolved to overcome current chemotherapeutic efforts [11].

Combinations of chemotherapeutics known as “chemo cocktails” hold the current standard for cancer treatment, however the compounded side effects, treatment delays, and sometimes dangerous drug-drug interactions make it less than an ideal solution [12]. Emerging evidence suggests that lidocaine may function as a chemosensitizer, meaning it can enhance the susceptibility of resistant cancer cell lines to anticancer agents. When used in conjunction with anti-cancer drugs such as cisplatin and 5-fluorouracil (5-FU), it can induce apoptosis by modulating signaling pathways (PI3K/AKT/mTOR), suppressing MAPK pathways, and inducing mitochondrial dysfunction [13]. It also has been shown to inhibit cancer cell survival pathways by suppressing ABC transporters and reducing promoter methylation of tumor suppressor genes (RARβ2 and RASSF1A) [14]. These abilities further support the potential for drug repositioning of lidocaine.

Current studies have shown lidocaine to exert its effects on multiple cancer cell lines with strong findings among those including lung, breast, liver, gastric, and colorectal lines [9, 4-17]. This is thought to be partly attributed to lidocaine's primary mechanism of action, VGSC inhibition. Cancer metastasis is known to be enhanced by VGSCs due to the regulation of extracellular pH and increased activity of enzymes that degrade the extracellular matrix (ECM) [18]. Metastasis seen in aggressive, solid cancer cells such as breast, prostate, and lung relies heavily on the downstream effects of VGSC activation, suggesting lidocaine may be able to influence tumor biology [19]. Despite these promising findings, the mechanisms and clinical relevance of lidocaine's anti-cancer effects remain incompletely understood.

This review aims to evaluate the potential of lidocaine as a repurposed therapeutic in oncology. Specifically, it will examine literature on the molecular mechanisms underlying lidocaine's anti-tumor effects. In addition, the review will explore current evidence surrounding its cellular effects in cancer models, with particular emphasis on mechanisms related to tumor progression, metastatic behavior, and inflammatory signaling. The capacity of lidocaine to enhance the efficacy of conventional chemotherapeutics and mitigate MDR will also be evaluated. Consideration will also be given to translational challenges and clinical implications of integrating lidocaine into existing cancer treatment strategies.

Background

Lidocaine and Cancer Cell Proliferation and Apoptosis

Lidocaine has demonstrated significant anti-proliferative and pro-apoptotic effects across various cancer cell lines, suggesting a direct role in inhibiting tumor growth. *In vitro* studies have shown that lidocaine exposure results in decreased cell viability and proliferation in cancers such as breast, lung, and colorectal [20-23]. Mechanistically, these effects are largely mediated by key intracellular signaling pathways involved in cell survival. Lidocaine has been shown to inhibit the PI3K/AKT/mTOR pathway (Figure 2) [24], a regulator of cell growth and proliferation that is frequently upregulated in malignant cells. In cancer cells, this pathway is dysregulated due to PI3K hyperactivity which leads to AKT (protein kinase B) activation and further mTOR (rapamycin) activation [25]. Inhibition of this pathway reduces downstream signaling required for protein synthesis and cell cycle progression, ultimately limiting tumor expansion. Additionally, various cancerous cell lines have been observed upregulating MAPK signaling pathways, resulting in increased proliferation and metastasis. Lidocaine yields inhibitory capabilities by suppressing the MAPK signaling cascade that is overexpressed in cancer cells. This is achieved by a down-regulation of phosphorylated ERK1/2 and activation of p38 MAPK (Figure 3) [26]. P38 MAPK in turn decreases cell proliferation, migration, and increases apoptosis, as seen by Li and colleagues when observing colorectal cancer (CRC) [23].

In addition to suppressing proliferation, lidocaine has been reported to induce apoptosis through influencing both intrinsic and extrinsic pathways. Evidence suggests that lidocaine promotes mitochondrial dysfunction, which is characterized by the loss of mitochondrial membrane potential and an increased release of cytochrome c into the cytosol. This subsequently activates mitochondrial proteases (caspase-9 and caspase-3), leading to a cleavage cascade ending in programmed cell death. Furthermore, lidocaine has been associated with alterations in the balance of pro- and anti-apoptotic proteins. The upregulation of BAX and downregulation of Bcl-2 seen favors apoptotic signaling in affected cells [27]. Repression of cytoskeleton formation via the inhibition of actin polymerization and disruption of F-actin distribution has also been observed as a mechanism lidocaine uses to decrease proliferation of cancer cells [28]. These molecular changes highlight lidocaine's ability to shift cancer cells away from survival and toward cell death.

Emerging research also suggests that lidocaine may exert epigenetic effects that contribute to its anti-cancer activity. Specifically, it has been shown to reduce promoter methylation of tumor suppressor genes such as RARβ2 and RASSF1A, leading to their re-expression in previously silenced cancer cells [15]. The restoration of tumor suppressor function further enhances apoptotic pathways and inhibits uncontrolled proliferation. Further, the upregulation of miR-145, a tumor suppressor MicroRNA which reduces Cyclin D1 and increases p21 resulting in an inhibition of cell growth and invasion, has been observed in cells treated with lidocaine [29]. Collectively, these findings indicate that lidocaine targets multiple regulatory systems involved in cancer cell survival, reinforcing its potential as a multi-faceted anti-cancer drug.

Lidocaine and Metastasis

Lidocaine has also been shown to inhibit cancer cell migration and metastasis, processes that are pertinent for cancer progression to occur. A key mechanism underlying this effect involves the inhibition of VGSCs. This is increasingly recognized with growing evidence showing their role in promoting metastatic behavior in cancer cells. VGSCs are often overexpressed in highly invasive cancers, including breast, prostate, colon, and lung tumors, where they contribute to enhanced cellular motility and invasion [30,31]. Their activity has been linked to the regulation of extracellular pH and the activation of proteolytic enzymes- such as matrix metalloproteinases (MMPs), which degrade the ECM and facilitate tumor cell dissemination (Figure 1) [32].

In cancerous cells, the increased intracellular sodium concentration due to hyperactive VGSCs alters the activity of other ion exchangers. Particularly, increasing Na^+/H^+ exchanger (NHE1) activity leading to an efflux of H^+ ions which results in further intracellular alkalinization and extracellular acidification. With respect to proteases, MMPs are activated and/or work more efficiently at lower pH. As a result, MMPs accelerate degradation of collagen and laminin stores that comprise the ECM. Additionally, sodium influx can influence calcium handling and kinase activity, resulting in actin filament remodeling and altered cell adhesion dynamics [28,33].

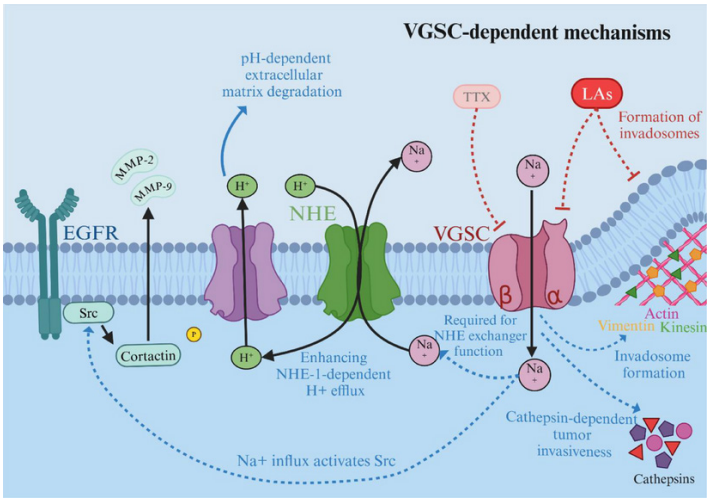

Figure 1: VGSC-dependent mechanisms. The increased VGSC activity leads to an increase in intracellular pH and decrease in extracellular pH via NHE1 activation [32].

By blocking VGSCs, lidocaine is thought to disrupt these pro-metastatic processes, reducing cancer cell invasiveness and migratory capacity. *In vitro* co-culture studies have demonstrated that lidocaine exposure leads to decreased cell migration and invasion, paralleled with reduced expression and activity of MMPs. Furthermore, lidocaine has been associated with alterations in cytoskeletal organization and cell adhesion dynamics, both of which are required for metastatic progression to occur. These findings suggest that lidocaine may interfere with multiple steps of the metastatic cascade, from local invasion to distant colonization. As metastasis remains the leading cause of cancer-related mortality, the ability of lidocaine to target VGSC-mediated pathways highlights its potential significance as an adjunct in limiting cancer spread [33].

Anti-inflammatory and Tumor Microenvironment

Chronic inflammation plays a role in tumor initiation, progression, and immune evasion, making the tumor microenvironment a high-value target in cancer therapy. Lidocaine has demonstrated the ability to modulate several important inflammatory pathways that contribute to tumor development. Notably, it inhibits the activation of NF-kB, which is a transcription factor that regulates the expression of numerous pro-inflammatory cytokines, adhesion molecules, and survival genes in cancer cells. Persistent activation of NF-kB is a hallmark of many malignancies and is associated with increased tumor growth, angiogenesis, and resistance to apoptosis [34,35]. Inhibition of NF-kB activation by lidocaine results in a decrease in cytokine release, lowering the overall physiologic inflammatory response.

In addition to NF-kB inhibition, lidocaine has been shown to suppress TLR signaling and reduce the release of inflammatory mediators such as TNF-α and HMGB1 [34]. These molecules are known to promote tumor-associated inflammation and facilitate

communication between cancer cells and their surrounding stromal and immune cells. By attenuating these signaling pathways, lidocaine may reduce the formation of a pro-tumorigenic microenvironment and enhance anti-tumor immune responses. Its effects on NK cell activity and cytokine signaling also suggest a potential role in preserving immune surveillance during cancer progression [35,36]. Together these anti-inflammatory and immunomodulatory properties position lidocaine as a promising candidate for tumor suppression.

Chemosensitization and Multi-drug Resistance

The development of MDR remains a major obstacle in effective cancer treatment, often leading to chemotherapy failure and disease recurrence. Lidocaine has emerged as a potential chemosensitizing agent capable of enhancing the efficacy of conventional chemotherapeutics [9]. One proposed mechanism involves the inhibition of ABC transporters, such as P-glycoprotein (ABCB1), MRP1, and BCRP, which actively efflux anti-cancer drugs out of cells and reduce intracellular drug accumulation. By suppressing the activity or expression of these transporters, lidocaine may increase the retention and effectiveness of chemotherapeutic agents within resistant cancer cells. Examples observed in experimental settings include: human breast cancer lines MCF-7 and MDA-MB-231, which were sensitized to cisplatin, SK-MEL-2 melanoma cells to 5-FU, BIU-87 human bladder cancer cells to Mitomycin C and Pirarubicin, and skin cancer cell lines and mucosal cancer cell lines to hyperthermia therapy by regulating cell cycle and heat shock proteins [9].

In addition to modulating drug efflux, lidocaine has been shown to influence key survival signaling pathways associated with chemoresistance (PI3K/AKT/mTOR and MAPK pathways) [9,37]. As discussed earlier, inhibition of these pathways can restore apoptotic sensitivity and reduce cellular mechanisms that promote survival under chemotherapeutic stress. *In vitro* and *in vivo* studies have also shown lidocaine to enhance the cytotoxic effects of commonly used agents such as cisplatin and 5-FU, leading to increased apoptosis and decreased proliferation compared to chemotherapy alone [9,38].

Further studies suggest that lidocaine may exert epigenetic effects that contribute to its chemosensitizing properties. For instance, reduced promoter methylation of tumor suppressor genes such as RARβ2 and RASSF1A have been observed following lidocaine treatment, resulting in their reactivation and increased susceptibility of cancer cells to chemotherapy-induced cell death [14]. These combined effects indicate that lidocaine targets multiple resistance mechanisms simultaneously, further reinforcing its potential value in overcoming MDR and improving therapeutic outcomes in cancer treatment.

Experimental and Clinical Studies

A growing body of experimental and clinical research supports the anti-cancer potential of lidocaine across multiple tumor types. *In vitro* studies have consistently demonstrated that lidocaine reduces cancer cell viability, proliferation, and migratory capacity in breast, lung, colorectal, and gastric cancer models [15-17,39]. For example, several *in vitro* studies have reported that lidocaine exposure leads to dose-dependent inhibition of proliferation and increased apoptotic activity, often associated with suppression of the PI3K/AKT/mTOR signaling pathway and activation of caspase-mediated cell death [9,17,27,38,40,41]. Ranxu and colleagues analyzed relevant publications between 2004-2024 and concluded findings that directly align with this review such as suppression of the PI3K/AKT/mTOR signaling pathway and inhibition of proliferation via alteration of MAPK pathways [40]. This further supports the notion that lidocaine directly interferes with key survival mechanisms in malignant cells.

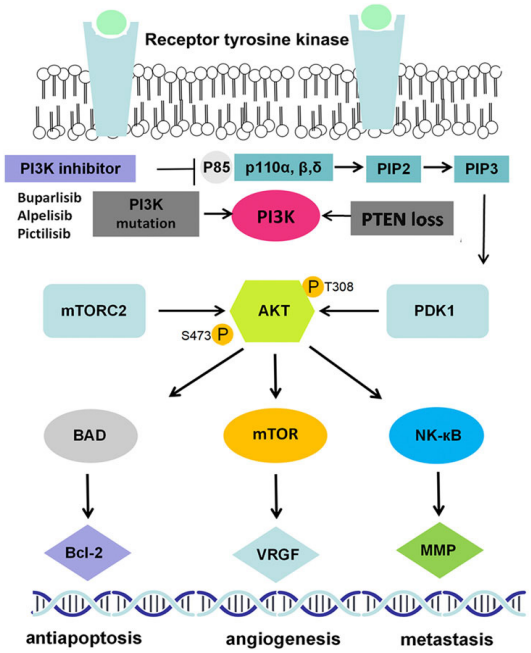

Figure 2: Activation of PI3K/AKT/mTOR pathway in breast cancer cells and the effects on cell proliferation and metastasis [24].

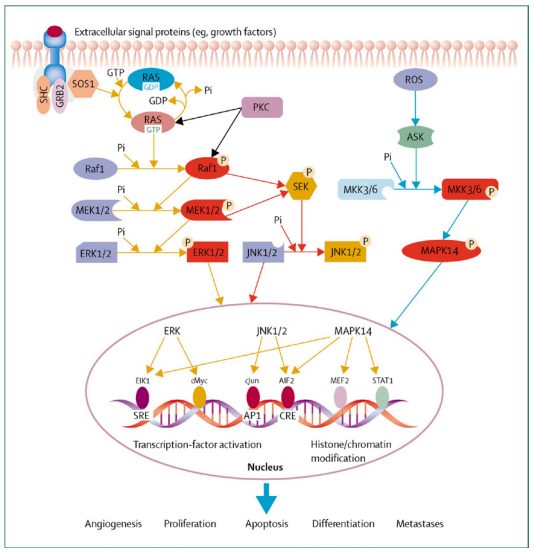

Figure 3: MAPK signaling pathway in colorectal cancer cells and its effects on cell proliferation, apoptosis, and metastasis [26].

In addition to its effects on proliferation, multiple studies have highlighted the role of lidocaine in inhibiting metastasis-related behaviors both *in vitro* and *in vivo*. Experimental models have shown that lidocaine reduces cancer cell migration and invasion through downregulation of MMPs and disruption of cytoskeletal organization. These effects are closely linked to the inhibition of VGSCs, which are overexpressed in highly metastatic cancers and contribute to the degradation of the ECM and tumor cell motility [9,42]. Such findings reinforce the mechanistic link between lidocaine's electrophysiological effects and its ability to suppress metastatic progression.

Lidocaine has also demonstrated synergistic effects when combined with conventional chemotherapeutic agents. Recent studies have investigated its use alongside drugs such as cisplatin and 5-FU and reported enhanced cytotoxicity, increased apoptosis, and reduced cancer cell survival compared to chemotherapy alone [43]. These effects are thought to result from lidocaine's ability to inhibit drug efflux transporters, modulate survival signaling pathways, and restore sensitivity to apoptotic signals as described by Wei et al. [43]. Furthermore, emerging evidence suggests that lidocaine may influence epigenetic regulation by reducing promoter methylation of tumor suppressor genes, enhancing the overall efficacy of chemotherapeutic treatment [15].

Freeman and colleagues provide evidence of the anti-cancer effects of lidocaine using a triple negative breast cancer mouse model. The mice were randomized into one of three groups: Sevoflurane/Control Group, Cisplatin Group, or Cisplatin and Lidocaine (C&L) Group. Results show that the C&L group had a >75% decrease in pulmonary metastatic colonies when compared to the other two groups. Additionally, reduced Interleukin-6 (IL-6) expression associated with perioperative lidocaine administration was observed, pointing to immune response depression and anti-inflammatory action. This evidence further supports the notion that lidocaine acts as a chemosensitizer as well as an immunomodulatory agent in cancer models. An important note is the primary tumor diameter was significantly increased for C&L treated mice compared to the control group [44]. This finding was not further explained by the text; however, it did not appear to make a difference in data interpretation.

In another mouse model exploring lidocaine's effects on bladder cancer, it was found that when combined with lidocaine, chemotherapeutic agent mitomycin C (MMC) more efficiently inhibited cell proliferation rates. The level of inhibition was found to be dose dependent, as seen with 22% inhibition with 1.25mg/mL lidocaine versus 74% inhibition with 5mg/mL lidocaine exposure. Yang et al. concluded that lidocaine in conjunction with other anti-cancer drugs (MMC) could potentially be a more effective therapy for bladder cancer than monotherapy [38].

Clinical evidence is more limited; however, it provides additional support for lidocaine's potential role as an anti-cancer drug. Several clinical trials exploring the anti-cancer effects of lidocaine have been completed and reported results that align with the notion that it can negatively influence cell metastasis and proliferation [36,45]. Notably, several ongoing clinical trials are actively investigating these effects [46-49]. Perioperative studies have suggested that intravenous lidocaine infusion during cancer surgery may be associated with reduced postoperative inflammation, preservation of immune function, and potentially lower rates of cancer recurrence [50-52]. However, these findings remain variable and are often derived from small or retrospective studies, which highlights the need for larger, well-defined clinical trials.

The available evidence on lidocaine's drug repositioning demonstrates that it exerts anti-cancer effects across multiple biological processes and experimental models. It is important to note that many *in vitro* studies utilize lidocaine concentrations exceeding those achievable in clinical settings, which raises concerns about translational applicability. Further, the variability in study design, dosing strategies and cancer types shows the need for standardized approaches in future research to better define its therapeutic potential.

Discussion

The growing body of evidence surrounding lidocaine's anti-cancer properties highlights its potential as a multi-targeted therapeutic agent in oncology. As discussed, lidocaine exerts effects across several hallmarks of cancer including the inhibition of proliferation, induction of apoptosis, suppression of metastasis, modulation of inflammatory signaling, and enhancement of chemosensitivity. These findings suggest that lidocaine does not act through a single pathway, but rather through a network of interconnected mechanisms that collectively disrupt tumor progression.

One of the most compelling aspects of lidocaine's anti-cancer activity is its ability to target VGSCs which are increasingly implicated in metastatic behavior. As previously discussed, VGSC inhibition plays a role in the limitation of metastatic cancer [53]. In parallel, its suppression of inflammatory pathways such as NF-kB and TLR signaling highlights its potential to alter the tumor microenvironment, which plays a key role in supporting tumor growth and immune evasion [54]. These combined effects give lidocaine a unique advantage as it can target both cancer cells directly, as well as the surrounding environment that facilitates their survival. Additionally, the ability of lidocaine to function as a chemosensitizer presents a promising strategy for overcoming MDR, which is a major limitation of current cancer therapies. By modulating drug efflux transporters, restoring apoptotic signaling, and influencing epigenetic regulation, lidocaine may enhance the efficacy of conventional chemotherapeutic agents such as cisplatin and 5-FU [33]. This is particularly significant given the clinical challenges associated with chemotherapy resistance- including treatment failure and disease recurrence.

Despite these findings, several challenges limit the integration of lidocaine into standard oncologic practice. A major barrier is the reliance on *in vitro* and preclinical models, which do not fully capture the complexity of human tumors and their

microenvironments. Also, many experimental studies utilize lidocaine concentrations that exceed those administered in clinical settings, raising concerns about the translational relevance to these findings [13]. Determining whether therapeutically safe doses can reproduce the observed anti-cancer effects remains a hurdle.

Pharmacokinetic and pharmacodynamic considerations also present challenges. Lidocaine has a relatively short half-life and is rapidly metabolized, which may limit its sustained anti-tumor activity when administered systemically. IV lidocaine peak plasma levels occur within 3-5 minutes, with a half-life of 30-120 minutes, compared to other local anesthetics such as bupivacaine (up to 5.5 hours) [55-57]. Building from this, its effects may vary depending on the route and timing of administration, particularly in perioperative versus long-term therapeutic contexts [58,59]. Optimizing delivery methods, such as continuous infusion, targeting delivery systems, or combination regimens, will enable clinicians to maximize its efficacy while minimizing systemic toxicity.

Another obstacle lies in the heterogeneity of cancer. Different tumor types, and even subpopulations within the same tumor, may exhibit variable expression of VGSCs, inflammatory mediators, and drug resistance mechanisms [60]. This variability suggests that lidocaine's effectiveness may not be universal, and that patient selection or biomarker identification will likely be necessary to determine which cancers are most responsive.

From a clinical perspective, there is currently a lack of large-scale, randomized controlled trials evaluating lidocaine's anti-cancer effects. While some perioperative studies have reported potential benefits, including reduced recurrence rates and preservation of immune function, findings remain inconsistent and insufficient to support widespread clinical adoption. Regulatory and logistical challenges associated with the repositioning of such an established drug as lidocaine may also slow its integration into oncology protocols [40,61].

Future research should therefore focus on bridging the gap between preclinical findings and clinical application. Well-designed clinical trials are needed to evaluate the efficacy of lidocaine in specific cancer types, both as a monotherapy and in combination with established chemotherapeutics. Attention should be given to identifying clinically relevant dosing and treatment windows. This is especially true in perioperative settings where lidocaine may influence metastatic spread.

Further investigation into the molecular mechanisms of lidocaine's action could help identify predictive biomarkers of response, enabling a more personalized approach to its use in oncology. Advances in drug delivery systems, such as nanoparticle-based carriers or targeted formulations, may also enhance its bioavailability and tumor-specific effects [62]. Finally, integrating lidocaine into combination therapies with immunotherapy or targeted agents represents a promising avenue for future exploration, given its immunomodulatory and anti-inflammatory properties. Overall, while lidocaine demonstrates significant potential as an anti-cancer drug, challenges remain. Addressing these limitations through focused and translational research will give insight into its potential role in cancer treatment.

Conclusions

In conclusion, lidocaine represents a compelling candidate for drug repositioning in oncology due to its diverse pharmacological profile and ability to target multiple hallmarks of cancer. Evidence from preclinical and emerging clinical studies indicates that lidocaine can inhibit cancer cell proliferation, induce apoptosis, suppress metastatic behavior through VGSC inhibition, modulate inflammatory signaling within the tumor microenvironment, and enhance the efficacy of conventional chemotherapeutic agents. These multifaceted effects distinguish lidocaine as a potentially valuable therapeutic, particularly in the context of overcoming multidrug resistance.

However, despite these promising findings, significant limitations currently restrict its clinical application. Most of the available evidence is derived from *in vitro* and preclinical models, with limited translation into well designed clinical trials. Uncertainty surrounding optimal dosage, route of administration, and pharmacokinetic constraints further complicates its integration into standard treatment protocols. Additionally, tumor heterogeneity and variability in molecular targets suggest that lidocaine's efficacy may be context dependent, making it necessary for more patient stratification in studies.

Further research should therefore prioritize the thoughtful design of clinical trials to evaluate lidocaine's therapeutic potential across specific cancer types and treatment settings. Efforts to establish clinically relevant doses, identify predictive biomarkers of response, and develop targeted delivery systems will be crucial to advancing lidocaine's drug repositioning. Moreover, exploring its role in combination therapies- including chemotherapy, immunotherapy, and targeted agents- may further enhance its clinical usability. While lidocaine alone is unlikely to replace conventional cancer therapies, its repositioning as an adjunctive agent offers a promising and cost-effective strategy to improve treatment outcomes. With continued investigation and clinical validation, lidocaine may emerge as a valuable component of integrated cancer treatment, particularly in addressing challenges such as metastasis and MDR.

References

1. Hollmann MW, Ritter CH, Henle P, et al. Inhibition of m3 muscarinic acetylcholine receptors by local anaesthetics. Br J Pharmacol. 2001; 133: 207-216. https://pmc.ncbi.nlm.nih.gov/articles/PMC1572757/#:~:text=In%20addition%2C%20m1%20and%20m3,receptor%20and%20coupled%20G%20protein
2. Weinberg L, Peake B, Tan C, et al. Pharmacokinetics and pharmacodynamics of lignocaine: A review. World J Anesthesiol. 2015; 4: 17-29. https://www.wjgnet.com/2218-6182/full/v4/i2/17.htm

3. Karnina R, Arif SK, Hatta M, et al. Molecular mechanisms of lidocaine. Annals of Medicine and Surgery. 2021; 69: 102733. https://www.sciencedirect.com/science/article/pii/S204908012100683X
4. Wu J, Chen Q, He Z, et al. Immunomodulatory Effects of Lidocaine: Mechanisms of Actions and Therapeutic Applications. Pharmaceuticals. 2026; 19: 134. https://pmc.ncbi.nlm.nih.gov/articles/PMC12845077/#:~:text=Signaling%20pathways%20regulated%20by%20lidocaine,%2C%20neutrophils%2C%20and%20T%20cells
5. Sasagawa S. Inhibitory effects of local anesthetics on migration, extracellular release of lysosomal enzyme, and superoxide anion production in human polymorphonuclear leukocytes. Immunopharmacol Immunotoxicol. 1991; 13: 607-622. https://pubmed.ncbi.nlm.nih.gov/1663527/
6. Bahar E, Yoon H. Lidocaine: A Local Anesthetic, Its Adverse Effects and Management. Medicina. 2021; 57: 782. https://pmc.ncbi.nlm.nih.gov/articles/PMC8399637/
7. Beecham GB, Nessel TA, Goyal A. Lidocaine. StatPearls. 2026. https://www.ncbi.nlm.nih.gov/books/NBK539881/
8. Yang X, Wei X, Mu Y, et al. A review of the mechanism of the central analgesic effect of lidocaine. Medicine (Baltimore). 2020; 99: e19898. https://pmc.ncbi.nlm.nih.gov/articles/PMC7440315/
9. Zhou D, Wang L, Cui Q, et al. Repositioning Lidocaine as an Anticancer Drug: The Role Beyond Anesthesia. Cell Dev Biol. 2020; 8. https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2020.00565/full
10. Ge M, Chen XY, Huang P, et al. Understanding and overcoming multidrug resistance in cancer. Nature Reviews Clinical Oncology. 2025; 22: 760-780. https://www.nature.com/articles/s41571-025-01059-1
11. Emran TB, Shahriar A, Mahmud AR, et al. Multidrug Resistance in Cancer: Understanding Molecular Mechanisms, Immunoprevention and Therapeutic Approaches. Front Oncol. 2022; 23: 891652. https://pmc.ncbi.nlm.nih.gov/articles/PMC9262248/#:~:text=In%20the%20field%20of%20cancer%20treatment%2C%20MDR,the%20concept%20commonly%20applied%20to%20antibiotic%20treatment
12. Hu Q, Sun W, Wang C, et al. Recent Advances of Cocktail Chemotherapy by Combination Drug Delivery Systems. Adv Drug Deliv Rev. 2015; 6: 19-34. https://pmc.ncbi.nlm.nih.gov/articles/PMC4998845/
13. Blazic A, Smerc R, Polajzer, et al. Reassessing lidocaine as an electroporation sensitizer in vitro. Sci Rep. 2025; 15: 25593. https://pmc.ncbi.nlm.nih.gov/articles/PMC12264040/#:~:text=Lidocaine's%20anticancer%20properties%20have%20been,NCT04162535%2C%20unknown%20status)50
14. Li K, Yang J, Han X. Lidocaine sensitizes the cytotoxicity of cisplatin in breast cancer cells via up-regulation of RARβ2 and RASSF1A demethylation. Int J Mol Sci. 2014; 15: 23519-23536. https://pubmed.ncbi.nlm.nih.gov/25526566/#:~:text=And%20a%20recent%20study%20has,cisplatin%20in%20breast%20cancer%20cells
15. Lirk P, Berger R, Hollmann MW, et al. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. British Journal of Anaesthesia. 2012; 109: 200-207. https://academic.oup.com/bja/article-abstract/109/2/200/253255
16. Ye L, Zhang Y, Chen YJ, et al. Anti-tumor effects of lidocaine on human gastric cancer cells in vitro. Bratisl Lek Listy. 2019; 120: 212-217. https://pubmed.ncbi.nlm.nih.gov/31023040/
17. Qu X, Yang L, Shi Q, et al. Lidocaine inhibits proliferation and induces apoptosis in colorectal cancer cells by upregulating mir-520a-3p and targeting EGFR. Pathology - Research and Practice. 2018; 214: 1974-1979. https://www.sciencedirect.com/science/article/pii/S0344033818309397
18. Brackenbury WJ, Djamgoz MBA, Isom LL. An emerging role for voltage-gated Na+ channels in cellular migration: Regulation of central nervous system development and potentiation of invasive cancers. Neuroscientist. 2008; 20: 571-583. https://pmc.ncbi.nlm.nih.gov/articles/PMC3380243/
19. Soto G, Calero F, Naranjo M. Lidocaine in oncological surgery: the role of blocking in voltage-gated sodium channels. Braz J Anesthesiol. 2020; 70: 527-533. https://pubmed.ncbi.nlm.nih.gov/32951865/#:~:text=A%20narrative%20review%20article%20discusses%20the%20role,involved%20in%20cell%20proliferation%2C%20migration%2C%20and%20metastasis
20. Sun Y, Liu B, Zhang X, et al. Lidocaine suppresses HER2-positive breast cancer cell proliferation by targeting the OGT-CCNL1 axis. Discov Oncol. 2025; 17. https://pmc.ncbi.nlm.nih.gov/articles/PMC12796022/#:~:text=Lidocaine%20is%20a%20local%20anesthetic%20and%20antiarrhythmic,Lung%20cancer%20*%20Hepatocellular%20carcinoma%20*%20Melanoma
21. Agostino GD, Saporito A, Cecchinato V, et al. Lidocaine inhibits cytoskeletal remodelling and human breast cancer cell migration. Br J Anaesth. 2018; 121: 962-968. https://pubmed.ncbi.nlm.nih.gov/30236259/
22. Zhang L, Hu R, Cheng Y, et al. Lidocaine inhibits the proliferation of lung cancer by regulating the expression of GOLT1A. Cell Prolif. 2017; 50: e12364. https://pmc.ncbi.nlm.nih.gov/articles/PMC6529060/#:~:text=Objectives,downstream%20molecular%20mechanism%20is%20unclear
23. Li W, Gao W, Lu C, et al. Lidocaine as a Potential Therapeutic Agent in Colorectal Cancer: A Study of Gene Expression and Prognosis. Onco Targets Ther. 2025; 18: 737-749. https://pmc.ncbi.nlm.nih.gov/articles/PMC12182729/#:~:text=Lidocaine%20significantly%20inhibited%20the%20proliferation,and%20optimize%20its%20clinical%20application
24. Dong C, Wu J, Chen Y, et al. Activation of PI3K/AKT/mTOR Pathway Causes Drug Resistance in Breast Cancer. Pharmacol. 2021; 12. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.628690/full

25. Glaviano A, Foo ASC, Lam HY, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Molecular Cancer. 2023; 22: 138. https://link.springer.com/article/10.1186/s12943-023-01827-6
26. Fang JY, Richardson BC. The MAPK signalling pathways and colorectal cancer. The Lancet Oncology. 2005; 6: 322-327. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(05)70168-6/abstract
27. Zhang C, Xie C, Lu Y. Local Anesthetic Lidocaine and Cancer: Insight Into Tumor Progression and Recurrence. 2021; 24: 669746. https://pmc.ncbi.nlm.nih.gov/articles/PMC8264592/
28. West R, Soo CP, Murphy J, et al. Cytoskeletal dynamics and F-actin redistribution changes induced by lidocaine in colon cancer cells: a fluorescence microscopy analysis. British Journal of Anaesthesia. 2024; 133: 469. https://www.bjanaesthesia.org/article/S0007-0912(24)00238-1/fulltext#
29. Sui HY, Lou A, Li Z, et al. Lidocaine inhibits growth, migration and invasion of gastric carcinoma cells by up-regulation of miR-145. BMC Cancer. 2019; 15: 233. https://pmc.ncbi.nlm.nih.gov/articles/PMC6419442/#:~:text=Lidocaine%20inhibited%20growth%20and%20metastasis,%2Dregulation%20of%20miR%2D145
30. Suzuki KH, Suzuki T, Nakasone C, et al. The local anesthetic, lidocaine, suppresses the growth of colon cancer SW480 cells by decreasing the voltage-gated sodium channel subunit Nav1.5. Scientific Reports. 2025; 15: 45018. https://www.nature.com/articles/s41598-025-29505-1
31. Soto G, Calero F, Naranjo M. Lidocaine in oncological surgery. Brazilian Journal of Anesthesiology. 2020; 70: 527-533. https://www.sciencedirect.com/science/article/pii/S0104001420301391
32. Rodriguez EN, Zhang H, Sah DK, et al. Intersection Between Local Anesthetics and Cancer Biology: What Now? Where Are We Going? Advanced Biology. 2025; 9. https://www.researchgate.net/figure/VGSC-dependent-mechanisms-affect-cancer-cell-invasion-and-metastasis-By-inhibiting-Nav_fig2_394385178
33. Zhou D, Wang L, Cui Q, et al. Repositioning Lidocaine as an Anticancer Drug: The Role Beyond Anesthesia. Front Cell Dev Biol. 2020; 17: 565. https://pmc.ncbi.nlm.nih.gov/articles/PMC7379838/
34. Soto G, Calero F, Naranjo M. Lidocaine in oncological surgery: the role of blocking in voltage-gated sodium channels. A narrative review. Brazilian Journal of Anesthesiology. 2020; 70: 527-533. https://bjan-sba.org/article/10.1016/j.bjane.2020.08.003/pdf/rba-70-5-527.pdf
35. Wu J, Chen Q, He Z, et al. Immunomodulatory Effects of Lidocaine: Mechanisms of Actions and Therapeutic Applications. Pharmaceuticals. 2026; 19: 134. https://pmc.ncbi.nlm.nih.gov/articles/PMC12845077/
36. Ramirez MF, Tran P, Cata JP. The Effect of Clinically Therapeutic Plasma Concentrations of Lidocaine on Natural Killer Cell Cytotoxicity. Perioperative Medicine. 40. https://rapm.bmj.com/content/40/1/43.abstract
37. Zhang Y, Jia J, Jin W, et al. Lidocaine inhibits the proliferation and invasion of hepatocellular carcinoma by downregulating USP14 induced PI3K/Akt pathway. Pathology - Research and Practice. 2020; 216: 152963. https://www.sciencedirect.com/science/article/abs/pii/S0344033819325464
38. Yang X, Zhao L, Li M, et al. Lidocaine enhances the effects of chemotherapeutic drugs against bladder cancer. Scientific Reports. 2018; 8: 598. https://www.nature.com/articles/s41598-017-19026-x
39. Tran TNC, Mathelin C, Aprahamian M, et al. Antitumor Effects of Lidocaine on Human Breast Cancer Cells: An In Vitro and In Vivo Experimental Trial. Anti Cancer Research. 2018; 38: 95-105. https://ar.iiarjournals.org/content/38/1/95.short
40. Lv R, Wang Y, Sun J, et al. The effect of lidocaine infusion in oncologic surgery: A bibliometric analysis based on CiteSpace. Systematic Review and Meta-Analysis. 2024; 103. https://journals.lww.com/md-journal/fulltext/2024/12200/the_effect_of_lidocaine_infusion_in_oncologic.1.aspx
41. Zhang C, Xie C, Lu Y. Local Anesthetic Lidocaine and Cancer: Insight Into Tumor Progression and Recurrence. Surgical Oncology. 2021; 11. https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2021.669746/full
42. Piegeler T, Schläpfer M, Dull RO, et al. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNFα-induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. British Journal of Anaesthesia. 2015; 115: 784-791. https://academic.oup.com/bja/article-abstract/115/5/784/230964
43. Wei X, Tai CD, Hao PJ, et al. Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells In Vitro and in a Xenograft Model In Vivo. Anesthesiology. 2017; 126: 868-881. https://www.ingentaconnect.com/content/wk/aln/2017/00000126/00000005/art00024
44. Freeman J, Crowley PD, Foley AG, et al. Effect of Perioperative Lidocaine and Cisplatin on Metastasis in a Murine Model of Breast Cancer Surgery. Anticancer Research. 2018; 38: 5599-5606. https://ar.iiarjournals.org/content/38/10/5599#:~:text=Establishing%20the%20tumor.,(MGS)%20(24).
45. https://clinicaltrials.gov/study/NCT05484687?cond=Cancer&term=Lidocaine&viewType=Card&rank=2&tab=researcher
46. https://clinicaltrials.gov/study/NCT04048278
47. https://clinicaltrials.gov/study/NCT04162535
48. https://clinicaltrials.gov/study/NCT01204242?cond=Cancer&term=Lidocaine&viewType=Card&page=2&rank=20
49. https://clinicaltrial.be/en/details/12271?only_active=0&only_eligible=0&only_recruiting=0&per_page=20
50. Wall TP, Buggy DJ. Perioperative Intravenous Lidocaine

and Metastatic Cancer Recurrence - A Narrative Review. Front Oncol. 2021; 11: 688896. https://pmc.ncbi.nlm.nih.gov/articles/PMC8365881/#:~:text=The%20amide%20local%20anaesthetic%20lidocaine,influence%20on%20postoperative%20cancer%20outcomes

51. Lv R, Wang Y, Sun J, et al. The effect of lidocaine infusion in oncologic surgery: A bibliometric analysis based on CiteSpace. Medicine. 2024; 103: e40980. https://pmc.ncbi.nlm.nih.gov/articles/PMC11666215/#:~:text=Abstract,Methods
52. Khan JS, Rai AS, Shanthanna H. The Overlooked and Misunderstood Analgesic: Considerations on the Perioperative Use of Intravenous Lidocaine. ASRA Pain Medicine. 2023. https://asra.com/news-publications/asra-newsletter/newsletter-item/asra-news/2023/02/01/the-overlooked-and-misunderstood-analgesic-considerations-on-the-perioperative-use-of-intravenous-lidocaine#:~:text=Emerging%20evidence%20also%20suggests%20that,with%20possible%20medical%2Dlegal%20repercussions
53. Rizaner N, Fraser SP, Gul IB, et al. Lidocaine Inhibits Rat Prostate Cancer Cell Invasiveness and Voltage-Gated Sodium Channel Expression in Plasma Membrane. The Journal of Membrane Biology. 2024; 257. https://www.researchgate.net/publication/377104427_Lidocaine_Inhibits_Rat_Prostate_Cancer_Cell_Invasiveness_and_Voltage-Gated_Sodium_Channel_Expression_in_Plasma_Membrane
54. Wu YY, Chen MS, Chen IC, et al. Lidocaine Modulates Cytokine Production and Reprograms the Tumor Immune Microenvironment to Enhance Anti-Tumor Immune Responses in Gastric Cancer. Int J Mol Sci. 2025; 26: 3236. https://pmc.ncbi.nlm.nih.gov/articles/PMC11989700/
55. https://www.clinpgx.org/pathway/PA166182313
56. Karnina R, Arif SK, Hatta M, et al. Molecular mechanisms of lidocaine. Annals of Medicine and Surgery. 2021; 69: 102733. https://www.sciencedirect.com/science/article/pii/S204908012100683X
57. https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/bupivacaine
58. Golzari SEJ, Soleimanpour H, Mahmoodpoor A, et al. Lidocaine and Pain Management in the Emergency Department: A Review Article. Anesth Pain Med. 2014; 4: e15444. https://pmc.ncbi.nlm.nih.gov/articles/PMC3961016/#:~:text=4.%20Conclusions.%20Lidocaine%20is%20a%20safe%20medication,anesthetic%20infiltration%2C%20digital%20blocks%20and%20hematoma%20blocks
59. Silva A, Mourao J, Vale N. A Review of the Lidocaine in the Perioperative Period. J Pers Med. 2023; 13: 1699. https://www.mdpi.com/2075-4426/13/12/1699
60. Jack ID, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol. 2018; 15: 81-94. https://pubmed.ncbi.nlm.nih.gov/29115304/
61. Saranraj K, Kiran PU. Drug repurposing: Clinical practices and regulatory pathways. Perspect Clin Res. 2024; 16: 61-68. https://pmc.ncbi.nlm.nih.gov/articles/PMC12048090/
62. Yang Y, Sun J, Peng F, et al. Enhanced Antitumor Activity of Lidocaine Nanoparticles Encapsulated by a Self-Assembling Peptide. Front Pharmacol. 2022; 13: 770892. https://pmc.ncbi.nlm.nih.gov/articles/PMC9068872/