

Anesthetics and cancer biology: Translational evidence from perioperative modulation to drug repurposing (Review)

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Abstract. Perioperative anesthesia is delivered during a brief but biologically dynamic interval in which surgical stress, inflammation, immune perturbation and tissue repair may alter the environment encountered by residual or disseminated tumor cells. Experimental studies indicate that anesthetic-related agents can modify proliferation, apoptosis, epithelial-mesenchymal transition, angiogenesis, immune surveillance and the tumor microenvironment. Translation to clinical benefit, however, has been inconsistent, in part because experimental models, routes and exposure schedules often differ substantially from perioperative pharmacology. Lidocaine and propofol illustrate this gap. In early breast cancer, a multicenter randomized trial reported improved 5-year disease-free and overall survival after preoperative peritumoral infiltration with 0.5% lidocaine, although independent confirmation is still required. By contrast, randomized comparisons of propofol-based and volatile anesthesia, including long-term follow-up studies and GA-CARES,

have not demonstrated an overall- or disease-free-survival advantage for propofol. Mechanistic and perioperative biomarker studies remain informative, but these biomarkers are not validated surrogates for oncological outcomes. This review therefore evaluates anesthetic-related interventions according to the exposure actually delivered, the level of mechanistic inference supported and the strength of clinical outcome evidence. Routine anesthetic choice should continue to follow established perioperative indications, whereas future cancer-directed studies should align clinically achievable exposure with defined biological mechanisms, selected patient populations and clinically meaningful endpoints.

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1. Introduction

Surgical resection remains a cornerstone of curative treatment for numerous solid tumors (1,2). Surgery, however, also creates a brief physiological disturbance marked by tissue injury, neuroendocrine activation, inflammation and altered immune function (3,4). Tumor manipulation and wound healing further reshape local and systemic signaling during this interval (5,6). Residual malignant cells and occult micrometastases may consequently encounter a host environment that differs

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substantially from the preoperative state. This temporal window provides a biologically plausible basis for asking whether perioperative interventions can influence tumor behavior, but plausibility alone does not show that anesthetic choice alters recurrence or long-term survival.

Previous reviews have generally organized the field by anesthetic technique, drug class, tumor type or immune mechanism (7-12). In the present review, the evidence is instead structured around the intervention that was actually delivered and the inference that each study design can reasonably support. Cellular and animal studies are considered in terms of target engagement, causal pathway evidence, exposure realism and context dependence; human biomarker studies are treated as pharmacodynamic evidence; and observational studies are kept distinct from randomized trials when clinical outcomes are discussed. This exposure-defined, inference-aware framework allows mechanistic and clinical findings to be considered together without obscuring important differences in route, model or endpoint. The abundance of mechanistic data has not been matched by consistent improvement in oncological outcomes. A randomized breast cancer trial found no reduction in recurrence with paravertebral-regional anesthesia plus propofol compared with sevoflurane-based general anesthesia and opioids (13). Randomized comparisons of propofol- and sevoflurane-based anesthesia, including long-term follow-up and General Anesthetics in Cancer Resection (GA-CARES), likewise found no overall- or disease-free-survival advantage for propofol (14,15). These findings define an important clinical boundary for interpreting favorable mechanistic observations.

A clearer interpretation also requires separation of three clinical contexts. Routine anesthetic care includes regional blockade, hypnotic selection, multimodal analgesia and opioid-sparing strategies chosen for established perioperative indications. Perioperative pharmacological modulation, by contrast, tests a defined agent, route and short exposure against a prespecified tumor- or host-response hypothesis. Cancer-directed repurposing is different again: It entails developing an anesthetic-related drug for an oncological indication, with an appropriate exposure strategy and evidence of clinical benefit. Because these settings differ in pharmacology, purpose and evidentiary threshold, each drug should be judged within the context in which it was actually studied.

2. The perioperative window: Biological plausibility and pharmacological distinctions

Cancer surgery generates a transient but complex physiological disturbance. Tissue injury, tumor manipulation, blood loss and pain activate sympathetic and hypothalamic-pituitary-adrenal signaling, accompanied by inflammatory and wound-healing responses (1,2,4,6,16). During the same period, experimental and translational studies have described reduced natural killer (NK)-cell activity, altered T-cell function and myeloid-mediated immunosuppression (3-6,16). These interacting perioperative influences are summarized in Fig. 1. Together, they may create a more permissive environment for residual or disseminated tumor cells. The premise is biologically credible; what remains uncertain is whether a perturbation lasting hours to days can materially affect recurrence or survival months or years later.

Perioperative interventions also create very different pharmacological exposures. Regional blockade and local infiltration act mainly at or near the source of nociceptive input and may attenuate the systemic stress response (17,18). Intravenous lidocaine, in contrast, produces a systemic exposure determined by bolus dose, infusion rate and duration (19). Propofol and volatile anesthetics are short-acting hypnotics whose exposure is largely restricted to the intraoperative period (20). Opioid-sparing strategies change the overall composition of perioperative analgesia rather than generating one discrete drug exposure, whereas experimental combination regimens introduce additional pharmacological interactions. Meaningful translation therefore requires explicit definition of route, duration and the biologically relevant exposure.

Technique-level comparisons complicate causal attribution because several components of care often change together. Regional vs. general anesthesia, or propofol-based total intravenous anesthesia vs. volatile maintenance, may simultaneously alter local-anesthetic exposure, opioid use, hypnotic selection, hemodynamic management and postoperative analgesia (21,22). An oncological effect therefore cannot readily be assigned to the anesthetic technique as a single entity. Individual agents are more informatively evaluated in relation to route, achievable exposure, relevant cellular compartment and observed phenotype.

3. Tumor-cell-intrinsic effects of anesthetic-related drugs

Within this perioperative setting, a large body of experimental work has examined whether anesthetic-related drugs act directly on malignant cells. Reported phenotypes include changes in proliferation, cell-cycle progression, apoptosis, autophagy, pyroptosis, epithelial-mesenchymal transition (EMT), invasion and stem-like behavior (23-26). These findings do not all carry the same weight. Much of the evidence derives from isolated cell lines or xenografts, with fewer studies performed in immune-competent systems, and experimental concentrations or exposure periods often differ from those encountered in perioperative care (27,28). A signaling change after drug exposure may reflect direct target engagement, a downstream pharmacodynamic response or a phenotype associated with some other initiating event. Dose, duration, tumor lineage and model system are therefore central to interpretation; selected pathway-level associations are summarized in Fig. 2.

Lidocaine. Among local anesthetics, lidocaine has generated the largest experimental literature in cancer biology. In breast cancer models, lidocaine exposure has been associated with reduced cytoskeletal remodeling and migration, with transient receptor potential melastatin 7 implicated in selected cell lines (29,30). In ovarian cancer, attenuation of metastatic phenotypes accompanied inhibition of NaV1.5-associated EMT and focal adhesion kinase (FAK)/Paxillin signaling (31). Prostate cancer models have likewise linked lidocaine to altered voltage-gated sodium channel (VGSC) expression and reduced invasiveness (32). Ion-channel signaling is therefore a plausible contributor to lidocaine activity, although it is unlikely to operate uniformly because VGSC expression and functional dependence vary across carcinomas (33).

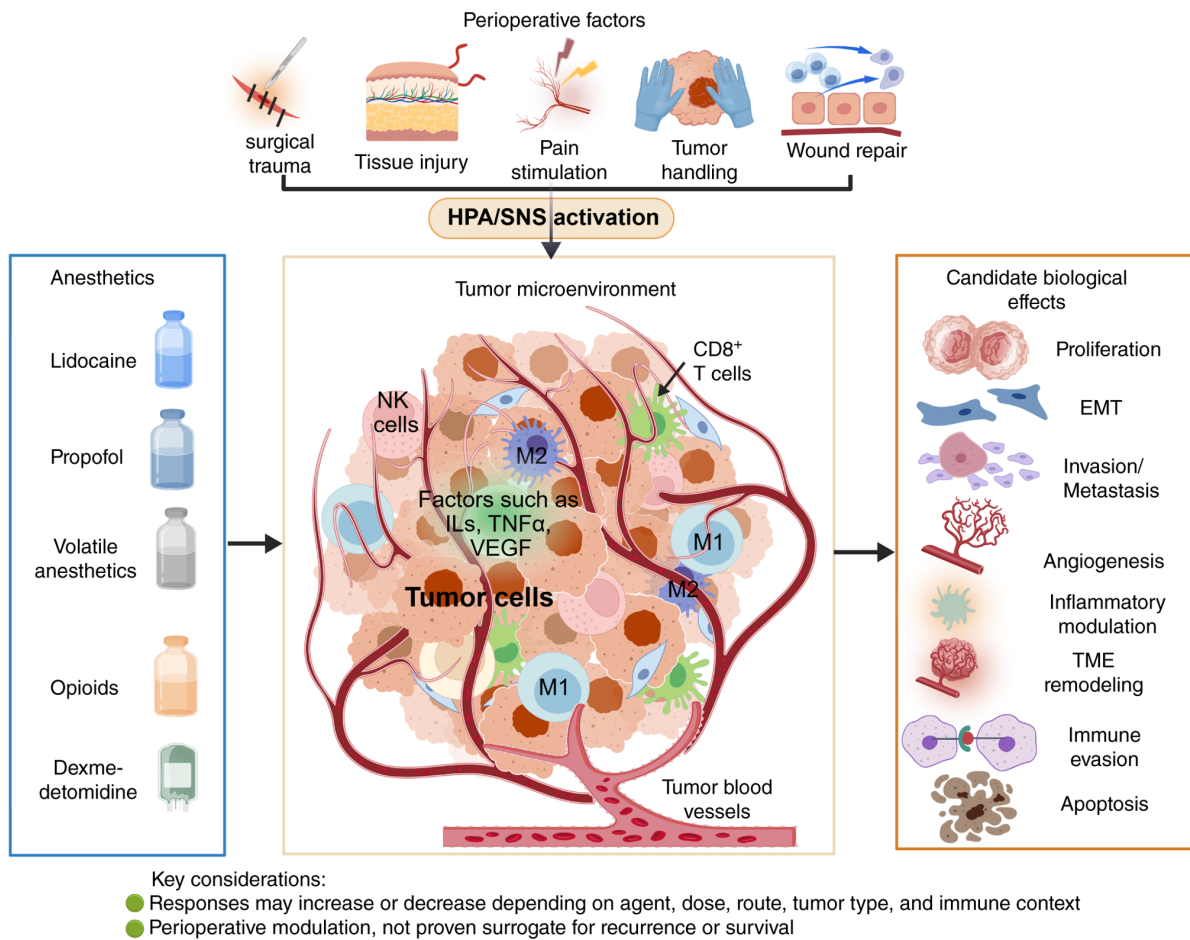


Figure 1. Perioperative interface between anesthetic-related interventions and cancer biology. Surgical stress and related perioperative factors activate the HPA axis and SNS and reshape the TME. Anesthetic-related agents may influence tumor cells, immune cells, inflammatory and angiogenic mediators, and tumor vasculature, with potential effects on proliferation, EMT, invasion/metastasis, angiogenesis, inflammation, immune evasion and apoptosis. These responses are context-dependent and are not validated surrogates for cancer recurrence or survival. EMT, epithelial-mesenchymal transition; HPA, hypothalamic-pituitary-adrenal axis; ILs, interleukins; M1/M2, macrophage polarization states; NK, natural killer; SNS, sympathetic nervous system; TME, tumor microenvironment; TNF- α , tumor necrosis factor- α ; VEGF, vascular endothelial growth factor.

A separate group of studies points to pathways governing adhesion and motility. Piegeler *et al* (23) reported that clinically relevant concentrations of lidocaine and ropivacaine suppressed tumor necrosis factor- α -induced invasion of lung adenocarcinoma cells, accompanied by reduced AKT and FAK activation. Lidocaine has also been tested together with Src inhibition in a murine model of breast cancer surgery (34), an observation of interest because Src is well established in focal-adhesion turnover, EMT, invasion and metastatic behavior (35). Under defined conditions, Akt, FAK and Src may therefore contribute to lidocaine-associated changes in cell motility. These experiments, however, do not establish any of these signaling proteins as direct molecular binding targets of lidocaine.

Epigenetic regulation has also been proposed as part of the response to lidocaine. In breast cancer cell lines, lidocaine induced DNA demethylation in a time- and dose-dependent manner (36). In a separate study, lidocaine enhanced cisplatin cytotoxicity while promoting demethylation and re-expression of retinoic acid receptor β 2 and Ras association domain family member 1A (37). Such findings raise the possibility that epigenetic regulation contributes to lidocaine-associated cellular effects. Whether a comparable process occurs

in human tumors during perioperative exposure remains unknown, particularly because the experimental concentrations and treatment periods have not been shown to reproduce clinically relevant changes in tumor DNA methylation.

Importantly, even within a single tumor lineage, the direction of response is not fixed. In A549 non-small cell lung cancer cells, Hsieh *et al* (38) observed EMT-associated changes and more aggressive behavior after lidocaine exposure, whereas another A549 study reported reduced migration through C-X-C chemokine receptor type 4-related regulation (39). Differences in concentration, exposure duration, inflammatory background, assay design or cellular state could account for the discrepancy. The most defensible interpretation is therefore that lidocaine acts as a context-dependent modulator of tumor-cell behavior rather than as a uniformly antitumor agent (40).

Propofol. Propofol presents a different translational challenge. Clinically, it is a short-acting intravenous hypnotic that produces a relatively brief, safety-limited systemic exposure, unlike local anesthetics that can be infiltrated into tissue or infused for longer periods. Experimental studies have associated propofol with changes in mitochondrial function, cellular

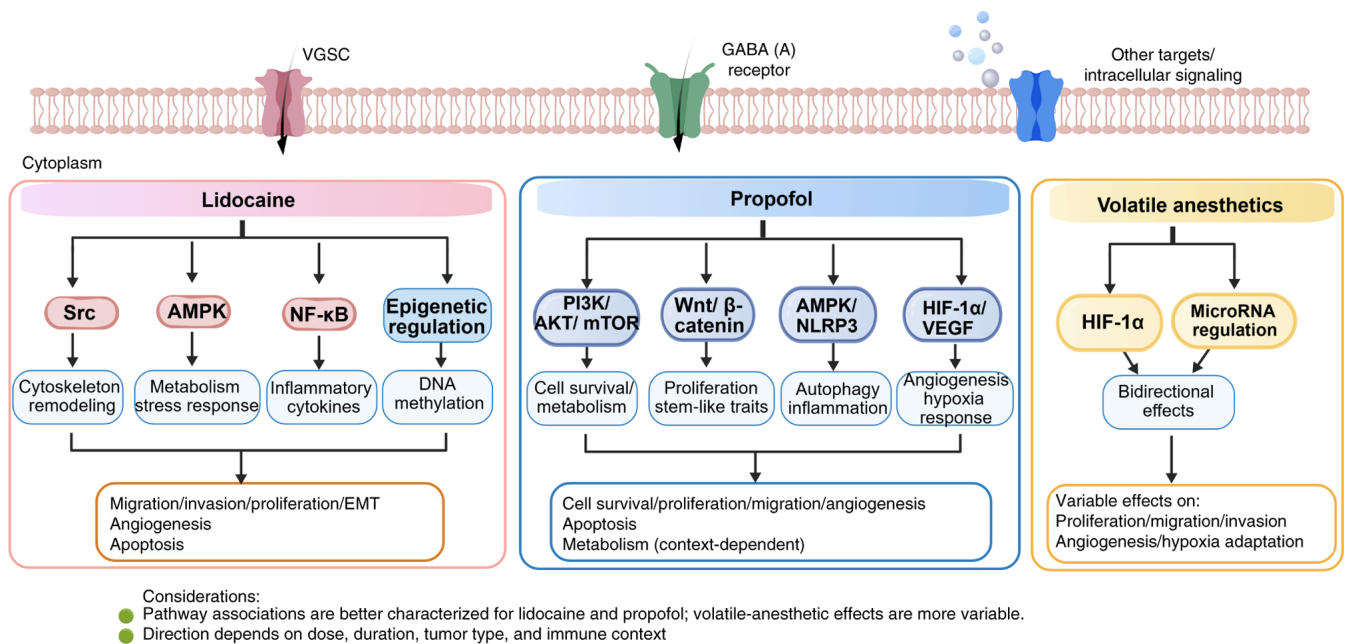


Figure 2. Selected molecular pathways associated with anesthetic-related agents in cancer models. The schematic summarizes reported signaling and phenotypic responses to lidocaine, propofol and volatile anesthetics, including VGSC-, PI3K/AKT/mTOR-, Wnt/ β -catenin-, AMPK-, NLRP3-, HIF-1 α /VEGF- and microRNA-associated pathways. Arrows indicate reported associations rather than uniformly established direct drug-target interactions; notably, the NLRP3 response reflects an immune-cell mechanism. Effects vary with exposure and biological context. AKT, protein kinase B; AMPK, AMP-activated protein kinase; EMT, epithelial-mesenchymal transition; GABA(A), γ -aminobutyric acid type A receptor; HIF-1 α , hypoxia-inducible factor-1 α ; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear factor- κ B; NLRP3, NLR family pyrin domain containing 3; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor; VGSC, voltage-gated sodium channel.

metabolism, inflammatory signaling and non-coding RNA (ncRNA) networks (41). Human perioperative studies have also reported differences in circulating extracellular-vesicle micro (mi)RNAs between propofol and sevoflurane anesthesia (42). These findings are biologically informative but are best interpreted as mechanistic or pharmacodynamic evidence rather than evidence of durable oncological benefit.

PI3K/AKT/mTOR signaling recurs prominently in the experimental literature. In liver and colorectal cancer (CRC) models, propofol has been associated with reduced AKT/mTOR activity, altered autophagy and attenuation of proliferation, invasion or stem-like phenotypes (43,44). Wnt/ β -catenin signaling has also been implicated in CRC, particularly in relation to EMT and cancer stem-like properties (44). The repeated appearance of these pathways does not imply a common upstream target. Rather, the initiating events appear to vary across experimental systems, and no single molecular target currently accounts for the range of responses reported across tumor types.

Interpretation becomes more complicated when the relevant signaling event occurs outside the malignant cell. Propofol activated adenosine monophosphate-activated protein kinase (AMPK) and suppressed HepG2 growth in an *in vitro*/xenograft study (45). By contrast, the widely cited NLR family pyrin domain containing 3 (NLRP3) study localized caspase-1-dependent pyroptosis to macrophages, making this an immune-cell rather than tumor-cell-intrinsic observation (46). Hypoxia-inducible factor-1 alpha (HIF-1 α)-associated responses have been described in selected lung cancer and angiogenesis models (47,48), with direction and magnitude influenced by hypoxia, inflammatory stimulation, drug

concentration and tumor type (49). Unless direct target engagement and causal dependence are demonstrated separately, AMPK, NLRP3 and HIF-1 α are better interpreted as components of reported pharmacodynamic responses than as established direct targets.

ncRNA studies add yet another layer of tumor specificity. Propofol has been linked to circular RNA/miRNA and long ncRNA regulatory networks in ovarian and esophageal cancer models (50-52), extending proposed mechanisms beyond canonical kinase signaling. Not all observations, however, point toward tumor suppression. In glioma, propofol enhanced stem-like properties through a γ -aminobutyric acid type A receptor-dependent SRC proto-oncogene, non-receptor tyrosine kinase (Src)/zDHHC palmitoyltransferase 5 (ZDHHC5)-enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) pathway (53). The propofol literature is therefore more accurately interpreted as a set of lineage- and context-dependent responses than as evidence for a broadly conserved anticancer program.

Volatile anesthetics, opioids and dexmedetomidine. The experimental literature is even more heterogeneous for volatile anesthetics. Isoflurane enhanced malignant phenotypes in renal cancer cells through HIF-1 α -related signaling *in vitro* (54), and modulation of the same pathway has been reported in prostate cancer models (55). In other systems, inhalational anesthetics suppressed proliferation or migration through specific miRNA-associated mechanisms, including studies in neuroglioma and glioma cells (56,57). These experiments differ substantially in agent, concentration, oxygen tension, tumor lineage and exposure duration. Volatile anesthetics therefore cannot be assigned a single oncological effect as a class.

Opioid-related tumor biology must be considered in light of the drugs' primary clinical role: Analgesia. Poorly controlled perioperative pain can amplify sympathetic and neuroendocrine activation, while experimental studies have linked μ -opioid receptor signaling, immune modulation and angiogenic pathways to tumor-associated phenotypes (58-61). The direction and magnitude of these effects vary with the opioid, dose, receptor expression and cancer context. Current evidence supports judicious opioid use within effective multimodal analgesia; broad opioid restriction intended specifically to improve oncological outcomes is not supported by clinical data (62).

Dexmedetomidine is similarly difficult to interpret as a purely tumor-cell-directed agent. Through α_2 -adrenergic agonism, it produces sympatholysis and modifies inflammatory and immune responses (63,64). In a surgically oriented A549 xenograft model, prolonged dexmedetomidine exposure was associated with slower tumor growth, reduced inflammation-related signaling and greater NK-cell activity (65). Clinical findings are less coherent. A recent meta-analysis found no overall-survival benefit in randomized studies, a recurrence-free-survival signal within those trials, and less favorable associations in retrospective cohorts (66). At present, these data do not support a defined cancer-directed therapeutic role for dexmedetomidine.

From molecular associations to translational interpretation. Table I maps representative studies by model, evidence type and inferential level. Direct molecular interaction, causal pathway dependence demonstrated by perturbation, downstream pharmacodynamic change and phenotype association support progressively different strengths of claim. A change in AKT phosphorylation, HIF-1 α abundance, miRNA expression or cell migration can establish that a system responded to exposure without identifying the molecular event through which the drug initially acted. Mechanistic interpretation should therefore consider the intervention, concentration, duration and model together with the experimental evidence for causal dependence.

Clinical studies address a complementary set of questions. A mechanism demonstrated at one concentration, by one route or in one tumor lineage may have limited relevance to a different exposure or disease setting. Conversely, a randomized trial can determine whether a defined perioperative intervention changes recurrence or survival even when the underlying molecular events are incompletely resolved. For this reason, direct interaction, causal pathway evidence, human pharmacodynamic activity and clinical efficacy are treated as distinct evidence categories throughout this review.

4. Tumor microenvironment and systemic host responses

Direct effects on malignant cells represent only one part of the anesthesia-cancer interface. During cancer surgery, tumor cells are embedded within a rapidly changing microenvironment shaped by immune surveillance, macrophage states, vascular signaling, neural input and stromal-tumor interactions (22,67,68). At the same time, wound healing, inflammation and neuroendocrine activation alter the systemic host milieu. These processes may influence the survival or

behavior of residual and disseminated tumor cells, but their clinical significance cannot be inferred from biomarker shifts alone. A perioperative change in an immune or inflammatory marker can demonstrate biological activity without predicting a durable effect on recurrence or survival.

Immune-cell function and macrophage polarization. Immune modulation has been studied most extensively with local anesthetics, particularly lidocaine. In preclinical models, Bezu *et al* (69) showed that the anticancer effects of local anesthetics could depend on an intact antitumor immune response. At clinically relevant concentrations, lidocaine enhanced NK-cell cytotoxicity *in vitro*, and related work reported increased NK-cell activity in cells obtained from patients undergoing cancer surgery (70,71). More recent experiments using tumor-infiltrating immune cells from gastric cancer extended these observations to cytokine regulation, M1-like macrophage polarization and NF- κ B-associated enhancement of CD8⁺ T-cell activity (72). Together, these data indicate that lidocaine can influence several components of antitumor immunity. Whether such immune changes contribute to clinical benefit remains uncertain, especially because intravenous, regional and peritumoral administration generate markedly different local and systemic exposures.

Propofol has also been associated with perioperative or *ex vivo* changes in NK-cell activity, cytotoxic T-cell function and inflammatory profiles (73-75). These studies demonstrate that anesthetic exposure can modify perioperative immune biology, but none of these readouts has been validated as a surrogate for recurrence or survival. Perioperative immune modulation and durable oncological benefit should therefore be considered separate outcomes unless a prospective link is established.

Inflammatory, angiogenic and neuro-tumor signaling. Inflammatory and vascular pathways provide another point of contact between anesthetic-related drugs and the tumor microenvironment. Lidocaine has suppressed vascular endothelial growth factor (VEGF)/VEGF receptor 2-associated angiogenic signaling in selected experimental models (76), whereas propofol has been linked to changes in VEGF-, mTOR- and HIF-1 α -related signaling in specific tumor systems (47,48). Volatile anesthetics have yielded less uniform effects, particularly in studies of hypoxia signaling and angiogenesis (54,55). Because the direction of response varies by agent, tumor model and experimental condition, these observations do not support a common anti-inflammatory or anti-angiogenic property of anesthetic drugs as a class.

Neural regulation intersects with both inflammatory and vascular mechanisms. In preclinical cancer models, β -adrenergic signaling can promote angiogenesis, immune suppression and metastatic behavior (77-79), prompting perioperative studies that target stress-related pathways rather than anesthesia alone. Small randomized trials combining β -adrenergic and cyclooxygenase-2 blockade in colorectal and breast cancer reported changes in biomarkers related to metastasis, inflammation, immunity and tumor proliferation (80-82). These studies show that the perioperative host environment is pharmacologically responsive. Whether such short-term modulation ultimately alters recurrence or survival remains unresolved.

Table I. Representative evidence by study type and inferential level.

Authors, year	Agent/intervention	Evidence type and model	Principal observation	Interpretation and source	(Refs.)
Piegeler <i>et al.</i> , 2015	Lidocaine	<i>In vitro</i> ; NCI-H838 lung adenocarcinoma	Lidocaine (1-100 μ M) reduced TNF- α -induced invasion and Akt/FAK activation.	Pathway-linked pharmacodynamic evidence; direct binding was not demonstrated.	(23)
Lirk <i>et al.</i> , 2012; Li <i>et al.</i> , 2014	Lidocaine	<i>In vitro</i> ; breast cancer cell lines	Time- and dose-dependent DNA demethylation; re-expression of RAR β 2 and RASSF1A was reported in a cisplatin study.	Epigenetic pharmacodynamic evidence; confirmation in human tumors is lacking.	(36,37)
Hsieh <i>et al.</i> , 2023; Xing <i>et al.</i> , 2022	Lidocaine	<i>In vitro</i> ; A549 NSCLC cells	EMT-associated aggressive behavior was reported in one study, whereas another found reduced CXCR4-related migration.	Divergent phenotype evidence within the same cell lineage; assay and exposure context are critical.	(38,39)
Bezu <i>et al.</i> , 2022	Local anesthetics	Immune-competent mouse and cellular models	Anticancer activity depended on an intact immune response.	Preclinical host-mechanism evidence; route and exposure remain model-specific.	(69)
Ramirez <i>et al.</i> , 2015; Cata <i>et al.</i> , 2017	Lidocaine	Human NK-cell <i>in vitro</i> / <i>ex vivo</i> studies	Clinically therapeutic plasma concentrations preserved or increased NK-cell cytotoxicity.	Human pharmacodynamic evidence; NK-cell activity is not a validated surrogate for recurrence.	(70,71)
Badwe <i>et al.</i> , 2023	Peritumoral lidocaine	Open-label multicenter RCT; early breast cancer	Five-year DFS, 86.6 vs. 82.6% (HR 0.74); OS, 90.1 vs. 86.4% (HR 0.71).	Route-specific clinical efficacy signal; the unblinded design, single disease setting and lack of independent confirmation limit extrapolation.	(85)
Chang <i>et al.</i> , 2022; Wang <i>et al.</i> , 2023; Wang <i>et al.</i> , 2020	Propofol	<i>In vitro</i> and xenograft; liver/colorectal cancer	Reduced AKT/mTOR activity, altered autophagy and attenuation of proliferative or stem-like phenotypes.	Pathway and phenotype evidence with model- and exposure-dependent relevance.	(43-45)
Sun <i>et al.</i> , 2019	Propofol	<i>In vitro</i> ; macrophages	Activated NLRP3-ASC signaling and caspase-1-dependent pyroptosis.	Mechanistically supported immune-cell effect; not a tumor-cell-intrinsic anticancer mechanism.	(46)
Fan <i>et al.</i> , 2022	Propofol	<i>In vitro</i> and xenograft; glioma	Enhanced stem-like traits through a GABA(A)R-Src-ZDHHC5-EZH2 pathway.	Causal, counter-directional preclinical evidence in a lineage-specific setting.	(53)
Buschmann <i>et al.</i> , 2020; Lim <i>et al.</i> , 2018; Apisitimaithi <i>et al.</i> , 2024; Wang <i>et al.</i> , 2023	Propofol vs. volatile anesthesia	Human perioperative biomarker studies	Differences were reported in extracellular-vesicle microRNAs, immune-cell assays and inflammatory transcriptomes.	Human pharmacodynamic evidence; links to recurrence or survival remain unvalidated.	(42,73, 75,89)

Table I. Continued.

Authors, year	Agent/intervention	Evidence type and model	Principal observation	Interpretation and source	(Refs.)
Cao <i>et al</i> , 2023; Bennett-Guerrero <i>et al</i> , 2026	Propofol vs. volatile anesthesia	Randomized clinical outcome trials	No improvement in OS or DFS with propofol-based anesthesia.	Current outcome evidence does not support routine anesthetic selection for oncological benefit.	(14,15)
Benzonana <i>et al</i> , 2013; Huang <i>et al</i> , 2014; Ishikawa <i>et al</i> , 2021; Zhao <i>et al</i> , 2020	Volatile anesthetics	<i>In vitro</i> ; renal, prostate and glioma models	HIF-1 α -related malignant phenotypes increased in some models, whereas microRNA-linked migration decreased in others.	Bidirectional, model-dependent phenotype evidence.	(54-57)
Sessler <i>et al</i> , 2019	Regional vs. general anesthesia	Randomized clinical out- come trial; breast cancer	Paravertebral-propofol anesthesia did not reduce recurrence (HR 0.97, 95% CI 0.74-1.28).	Bundled perioperative technique with no demonstrated recurrence advantage.	(13)

The entries illustrate selected evidence types rather than a formal grading system. The inference supported by each study depends on mechanistic depth, exposure realism, biological context and the clinical endpoint assessed. CI, confidence interval; DFS, disease-free survival; EMT, epithelial-mesenchymal transition; FAK, focal adhesion kinase; HR, hazard ratio; NK, natural killer; NSCLC, non-small cell lung cancer; OS, overall survival; RCT, randomized controlled trial.

Integrated regulation of the perioperative host response. The perioperative host response cannot be reduced to a single anesthetic exposure. Surgical injury, analgesia, transfusion, temperature, hemodynamic changes and inflammatory signaling occur concurrently and interact throughout the perioperative period (10,62,83). This biological and clinical overlap makes it difficult to attribute a change in immunity or tumor-related signaling to one component of anesthetic management in isolation. Regional anesthesia and opioid-sparing approaches remain valuable for analgesia, recovery and perioperative care, but evidence that they alter cancer outcomes is inconsistent (13,84). A perioperative biomarker response alone does not establish disease modification. Translational relevance therefore requires a pharmacologically defined exposure, a reproducible biological response and clinically meaningful outcome data.

5. Drug-specific translational appraisal

The qualitative appraisal used here considers six linked features: Reproducibility across models, mechanistic depth, compatibility with clinically achievable exposure, evidence of human pharmacodynamic activity, randomized oncological outcomes and feasibility of the proposed route and schedule. This framework is deliberately exposure-specific and is not intended as a standardized evidence grade. The six features may point in different directions. A drug can have an extensive mechanistic literature yet little evidence of long-term clinical benefit; conversely, a favorable outcome obtained with one highly specific route may provide little information about other modes of administration. This distinction is especially important when local anesthetics are compared with propofol, volatile anesthetics, opioids and dexmedetomidine.

Local anesthetics. Among the agents considered, lidocaine is notable for a positive randomized clinical signal, although that signal is tightly linked to the route that was tested. In the multi-center open-label trial by Badwe *et al* (85), women with early breast cancer undergoing upfront surgery received peritumoral 0.5% lidocaine 7-10 min before tumor resection or no lidocaine. After a median follow-up of 68 months, 5-year disease-free survival was 86.6% in the lidocaine group and 82.6% in the control group [hazard ratio (HR) 0.74, 95% CI 0.58-0.95; P=0.017]. Furthermore, 5-year overall survival was 90.1 and 86.4%, respectively (HR 0.71, 95% CI 0.53-0.94; P=0.019) (85). The difference is clinically important, but its interpretation remains bounded by the open-label design, the selected early breast cancer population, the immediate preoperative peritumoral route and the absence of independent replication with survival endpoints. Whether intravenous lidocaine or regional anesthesia can reproduce this result remains elusive.

Other local anesthetics illustrate how readily experimental responses can vary by compound and model. Ropivacaine has inhibited invasion or tumor growth in selected lung adenocarcinoma and melanoma systems, whereas bupivacaine has shown activity in ovarian and prostate cancer models but not in the melanoma model in which lidocaine and ropivacaine were effective (23,86-88). Broad class-wide extrapolation is therefore difficult. For any individual agent, translational potential will depend on whether an active exposure is achievable through a feasible clinical route, whether that exposure elicits

a measurable biological response in patients and whether the response is linked to a meaningful oncological outcome without unacceptable toxicity.

Propofol. Propofol presents a contrasting translational profile, with an extensive experimental literature but largely neutral randomized evidence for long-term cancer outcomes. In the multicenter follow-up reported by Cao *et al* (14), 1,195 patients were included in the modified intention-to-treat analysis. Overall survival did not differ between propofol-based anesthesia and sevoflurane (adjusted HR 1.02, 95% CI 0.83-1.26; $P=0.834$), and recurrence-free survival was also comparable (adjusted HR 1.07, 95% CI 0.89-1.30; $P=0.465$) (14). GA-CARES produced a similar overall result: Propofol was not associated with improved overall survival in the intention-to-treat population (HR 1.16, 95% CI 0.96-1.41; $P=0.115$), and disease-free survival was likewise not improved (HR 1.10, 95% CI 0.90-1.36; $P=0.428$) (15). Human mechanistic studies may still inform future hypothesis development. Propofol exposure has been associated with differences in immune function, circulating extracellular-vesicle miRNAs and perioperative transcriptomic responses (42,73,89). These studies are useful for defining candidate pharmacodynamic readouts, but cancer-directed use would require a distinct indication and exposure strategy supported by clinical evidence.

Volatile anesthetics, opioids and dexmedetomidine. Volatile anesthetics have produced bidirectional, model-dependent preclinical findings, including HIF-1 α - and miRNA-associated effects (54-57). This heterogeneity, together with the absence of a clear clinical outcome signal, provides no oncological basis for their routine avoidance or preferential selection. Opioid-related findings remain difficult to separate from analgesic indication, dose, μ -opioid receptor biology, tumor context and the consequences of inadequate pain control (59,62,90). Current cancer-outcome data do not support broad opioid restriction; effective multimodal analgesia and avoidance of unnecessary exposure remain appropriate. Dexmedetomidine is best viewed as a host-response modifier used for established perioperative indications. Although preclinical studies suggest effects on tumor growth and antitumor immunity (65), clinical outcome data remain inconsistent (66) and do not establish a cancer-directed role.

Translational positioning across agents. Translational positioning is exposure-specific. The randomized lidocaine signal is confined to preoperative peritumoral use in early breast cancer and remains unconfirmed (85), whereas randomized propofol trials have shown no oncological advantage over volatile anesthesia (14,15). Evidence for volatile anesthetics, opioids and dexmedetomidine remains mainly context dependent or clinically inconsistent. Route, duration, achievable concentration, tumor setting and endpoint therefore determine what can be inferred from each intervention; findings from one exposure should not be generalized to another.

6. Why preclinical signals have not translated consistently

Preclinical-clinical discordance often reflects differences in exposure, model biology and clinical context rather than

a simple contradiction. Experimental effects may require concentrations, durations or routes not achieved perioperatively, while tumor genotype and host immunity can modify the response. In patients, any anesthetic effect is superimposed on surgery, disease stage, resection quality, perioperative care and subsequent oncological treatment; even genuine biological modulation may be too small or transient to alter long-term outcomes.

Exposure, route and duration. Pharmacological exposure is among the most immediate sources of mismatch between experimental systems and perioperative practice. Lidocaine illustrates the problem well. Tumescence administration has absorption kinetics that differ substantially from those of intravenous infusion (91). In the LOLIPOP breast cancer pilot trial, lidocaine was given as a 1.5 mg/kg intravenous bolus followed by a 2 mg/kg/h intraoperative infusion and then a 1.33 mg/kg/h subcutaneous infusion for up to 12 h; serum concentrations changed across these phases of administration (92,93). Marked interindividual variability has also been documented during intravenous lidocaine infusion in colorectal surgery (94). Nominal concentration values are meaningful only within their pharmacological setting. The concentration of an infiltration solution, a measured plasma concentration, the unbound plasma concentration and the nominal concentration applied to cultured cells are not interchangeable quantities. Propofol adds the constraints of brief clinical administration and extensive protein binding, so total experimental concentrations may poorly represent the free drug available for tissue distribution *in vivo* (20,95,96).

Table II places representative exposure values alongside their route, duration and model. Peritumoral 0.5% lidocaine, for example, was injected around the tumor 7-10 min before surgery, yet the corresponding intratumoral and systemic drug concentrations were not established (85). The clinical result should therefore be interpreted as evidence for that specific local, short-duration intervention. Numerical overlap between experimental and clinical reports becomes informative only when route, time course, relevant tissue exposure and free-drug fraction are sufficiently comparable.

Model and tumor-context limitations. Exposure mismatch is only one part of the problem. Conventional two-dimensional cell lines and immunodeficient xenografts remain useful for identifying candidate pathways, but they reproduce only a fraction of human tumor biology. Tumor architecture, stromal gradients, vascular organization, intact immunity and the physiological disturbance produced by surgery are incompletely represented in these systems (97-99). This limitation becomes particularly important when the proposed mechanism depends on macrophages, NK cells, T cells, vascular cells or neural signaling (67,68). A tumor-cell response observed in isolation may change substantially once immune and stromal compartments are restored. Tumor lineage, molecular subtype, driver genotype, oxygen tension and baseline inflammatory state can likewise alter both the magnitude and the direction of a drug response.

Greater biological realism does not require abandoning reductionist models; it requires matching each model to the question it can answer (97-99). Dose-response and time-course

Table II. Representative exposure examples illustrating the limits of cross-setting concentration comparisons.

Authors, year	Agent	Setting/model	Nominal exposure	Route/duration	Interpretation and source	(Refs.)
Piegeler <i>et al</i> , 2015	Lidocaine	NCL-H838 cells	1-100 μ M	Nominal culture concentration	Assay-specific cellular exposure; not directly equivalent to plasma or tissue exposure.	(23)
Toner <i>et al</i> , 2021;	Lidocaine	LOLIPOP breast cancer trial	1.5 mg/kg bolus; 2 mg/kg/h IV; then 1.33 mg/kg/h SC	Perioperative infusion; SC phase up to 12 h	Serum concentrations changed by administration phase and showed interpatient variability.	(92,93)
Greenwood <i>et al</i> , 2019	Lidocaine	Colorectal surgery	Mean plasma 3.2 vs. 4.6 μ g/ml	Lower-vs. higher-dose IV regimens	Measured clinical plasma exposure varied with regimen and patient factors.	(94)
Badwe <i>et al</i> , 2023	Lidocaine	Early breast cancer RCT	0.5% infiltration solution	Peritumoral injection 7-10 min before surgery	Local solution concentrations; tumor-tissue and systemic concentrations were not established.	(85)
Chhabra <i>et al</i> , 2022	Propofol	Target-controlled sedation	Mean target 1.13 $\pm$ 0.17 μ g/ml; 85% at $\leq$ 1.2 μ g/ml	Clinical plasma-target concentration	A sedation target under neuraxial anesthesia; it does not define tumor exposure during general anesthesia.	(95)
Mazoit <i>et al</i> , 1999	Propofol	Whole-blood binding study	Total 0.5-32 μ g/ml; free fraction 1.2-1.7%	Concentration-dependent binding assessment	Total concentration substantially exceeds the unbound drug available for distribution.	(96)
Benzonana <i>et al</i> , 2013	Isoflurane	Renal cancer cells	0.5-2%	2h <i>in vitro</i> gas exposure	Delivered gas percentage is not interchangeable with a tissue or plasma concentration.	(54)

Values are specific to the cited route and model and should not be interpreted as equivalent exposures. Solution concentration, measured plasma concentration, free concentration, gas percentage and nominal culture concentration represent distinct pharmacological quantities. IV, intravenous; SC, subcutaneous.

experiments are well suited to defining exposure dependence, whereas immune-competent systems and patient-derived models become more informative when host-tumor interactions are central to the proposed mechanism (36,98,99). In anesthesia-cancer research, these variables are not minor experimental details. They may determine whether a reported phenotype is reproducible at all (38,39).

Clinical heterogeneity, confounding and endpoint selection. Clinical studies introduce a different layer of heterogeneity. Patients undergoing cancer surgery differ in tumor stage and subtype, surgical extent, regional analgesia, opioid and corticosteroid exposure, transfusion requirements, hemodynamic management and postoperative anticancer treatment (21,28,100). Many of these factors can influence inflammatory and immune responses independently of the anesthetic agent under study (16,21,28). Technique-level comparisons are especially difficult to interpret because several elements of perioperative care often change together. Switching from volatile anesthesia to propofol-based total intravenous anesthesia, or from general anesthesia alone to a regional technique, may simultaneously alter opioid consumption, local-anesthetic exposure, postoperative analgesia and hemodynamic management (8,13,21,28). Any cancer-related signal is therefore superimposed on a broader perioperative treatment package, limiting attribution to a single exposure (8,16).

Recurrence and overall survival remain the outcomes of greatest clinical importance, but neither is determined by perioperative biology alone (28,100). Surgical completeness, tumor aggressiveness, systemic therapy, radiotherapy and subsequent disease management exert major and more sustained effects on long-term outcome (16,21,28,100). Early clinical studies can still use prespecified pharmacodynamic endpoints to determine whether an intervention engages the intended biological process (28). Such endpoints are valuable for demonstrating activity; they do not replace recurrence or survival when the clinical question is durable cancer control.

Context dependence and bidirectional effects. A further challenge is that anesthetic-related effects are not consistently unidirectional. Lidocaine has been associated with reduced invasion in certain lung cancer experiments, yet EMT-associated and more aggressive phenotypes have been reported under different conditions (23,38,39). Propofol has produced numerous tumor-suppressive phenotypes in cell models, while a mechanistically detailed glioma study showed enhanced stem-like properties through a γ -aminobutyric acid type A receptor/Src/ZDHHC5-EZH2 pathway (53). Volatile anesthetics show a similar pattern: HIF-1 α -related adaptation may be enhanced in one system, whereas migration is suppressed through miRNA-dependent mechanisms in another (54,56). Representative counter-directional and host-level responses are summarized in Fig. 3.

These apparent contradictions are informative rather than simply inconsistent. Drug concentration, exposure duration, tumor lineage, genotype, inflammatory state, oxygen tension and immune context can shift the same signaling network toward different phenotypic outcomes. Reducing a finding to a binary ‘pro-’ or ‘anti-tumor’ label obscures the

experimental conditions most likely to determine its translational relevance. Host-directed effects introduce an additional layer of complexity. Opioid-related immunomodulation remains biologically plausible, but inadequate analgesia can itself intensify sympathetic and neuroendocrine stress, and observational associations are vulnerable to confounding by indication and disease severity (62,90). Similar concerns arise whenever perioperative drugs are studied outside the clinical context in which they are ordinarily used. For a preclinical signal to acquire translational significance, it should persist at a safely achievable exposure, remain reproducible in an appropriate tumor and host context, and be detectable in humans through a relevant pharmacodynamic response. Whether that response materially contributes to recurrence or survival is a separate question. Bridging this gap requires experimental systems that preserve mechanistic resolution while more closely reproducing human tumor biology and clinically realistic drug exposure.

7. Experimental platforms for mechanism-informed translation

Patient-derived organoids (PDOs), immune cocultures, tumor-on-chip platforms and multi-omics technologies can place a defined drug exposure within a more representative cellular, spatial and pharmacological context (101-103). Each addresses a different limitation of conventional models. Organoids retain selected patient-specific tumor features; immune cocultures permit direct interrogation of host-tumor interactions; and microphysiological systems can reproduce gradients, perfusion and tissue interfaces. Their utility depends on matching the platform to the proposed mechanism, route and clinically plausible exposure. These systems serve as intermediate tools for mechanistic validation, not as evidence of clinical efficacy in their own right (104-106).

Organoids, immune cocultures and tumor-on-chip models. PDOs preserve important genomic features of the original tumor and part of its intratumoral heterogeneity (99,101-103). Immune cocultures can incorporate immune and stromal components, whereas tumor-on-chip systems can reproduce perfusion and spatial gradients that are largely absent from conventional two-dimensional culture (104,105). These platforms are particularly relevant to anesthesia-cancer research, where drug effects may depend on transient exposure, tissue distribution, immune-cell interactions or local microenvironmental conditions. They can reproduce clinically realistic exposure schedules while allowing target engagement, pathway activity and tumor-host interactions to be examined within a single framework, and can test whether a response observed in a homogeneous cell line persists across patient-derived tumors or is restricted to a particular molecular background. Even so, activity in an organoid or microfluidic system does not establish therapeutic efficacy; translational relevance depends on clinically achievable exposure and a measurable human correlate.

Single-cell, spatial and microbiome approaches. Single-cell and spatial profiling offer a different advantage: They can identify the cellular compartment in which a drug-associated response occurs (106). A change attributed broadly to ‘tumor

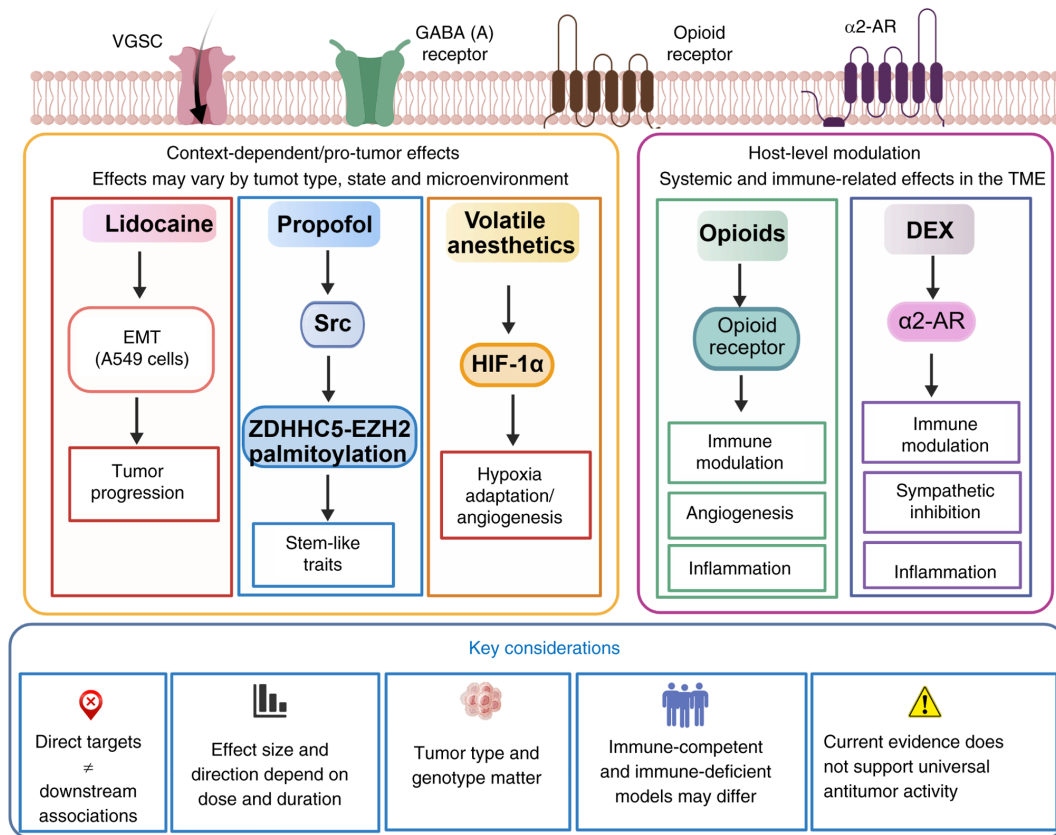


Figure 3. Context-dependent and host-mediated responses to anesthetic-related drugs. Representative context-dependent findings include lidocaine-associated EMT in A549 cells, propofol-associated Src/ZDHHC5-EZH2 signaling and stem-like traits in glioma and HIF-1 α -associated responses to volatile anesthetics. Opioids and dexmedetomidine additionally modulate immune, inflammatory, angiogenic and sympathetic pathways at the host level. Downstream associations should not be interpreted as direct molecular targets and the direction of response varies with exposure, tumor and immune context. α 2-AR, α 2-adrenergic receptor; DEX, dexmedetomidine; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; GABA(A), γ -aminobutyric acid type A receptor; HIF-1 α , hypoxia-inducible factor-1 α ; VGSC, voltage-gated sodium channel; ZDHHC5, zinc finger DHHC-type palmitoyltransferase 5.

tissue' may originate from malignant cells, macrophages, endothelial cells, neural elements, fibroblasts or other stromal populations, and these technologies can distinguish among them (107-109). This level of resolution is especially useful when the same anesthetic-related drug produces apparently divergent effects across tumor models or when a host-mediated mechanism is suspected. Microbiome research remains at an earlier stage. The gut microbiota is increasingly recognized as a determinant of response to cancer immunotherapy (110), and perioperative management may alter microbial composition and function (111). Reproducible pharmacodynamic relationships between specific anesthetic agents and microbiome-mediated cancer outcomes, however, have not been established. For now, microbiome, single-cell and spatial approaches are most useful for locating responsive biological compartments, refining mechanistic hypotheses and defining patient subgroups in which an effect may be more likely to emerge. Their contribution to anesthetic drug repurposing will depend on linking these molecular patterns to a specific exposure and, ultimately, to clinical outcomes.

8. Designing the next generation of clinical studies

Clinical development should begin with a pharmacologically defined exposure and evidence of target engagement or a proximal biological response. Fig. 4 separates perioperative

modulation from cancer-directed repurposing within this staged framework. Because many perioperative changes are transient, protocols should prospectively align the drug, route, dose, duration, biological hypothesis, sampling schedule and endpoint. Biomarkers should be prespecified as pharmacodynamic, prognostic, predictive or surrogate measures; their use as surrogates requires independent validation.

Mechanism-based and exposure-defined trials. Lidocaine provides a clear example of why route should not be treated as a minor design variable. Peritumoral injection, intravenous infusion, regional blockade and local infiltration produce markedly different tissue and systemic exposures. Trials prompted by the findings of Badwe *et al* (85) are most informative when they reproduce the peritumoral regimen or deliberately test how changes in dose, route or timing alter the biological and clinical effect. Evidence generated with intravenous lidocaine should not be assumed to represent the same intervention.

The same distinction applies to propofol. Routine intraoperative maintenance creates a short, safety-limited exposure and should be conceptually separated from any strategy that develops propofol as a cancer-directed pharmacological intervention. Existing randomized trials have not demonstrated a survival advantage for conventional propofol-based anesthesia (14,15), which places clear boundaries around hypotheses derived from preclinical studies. If cancer-specific

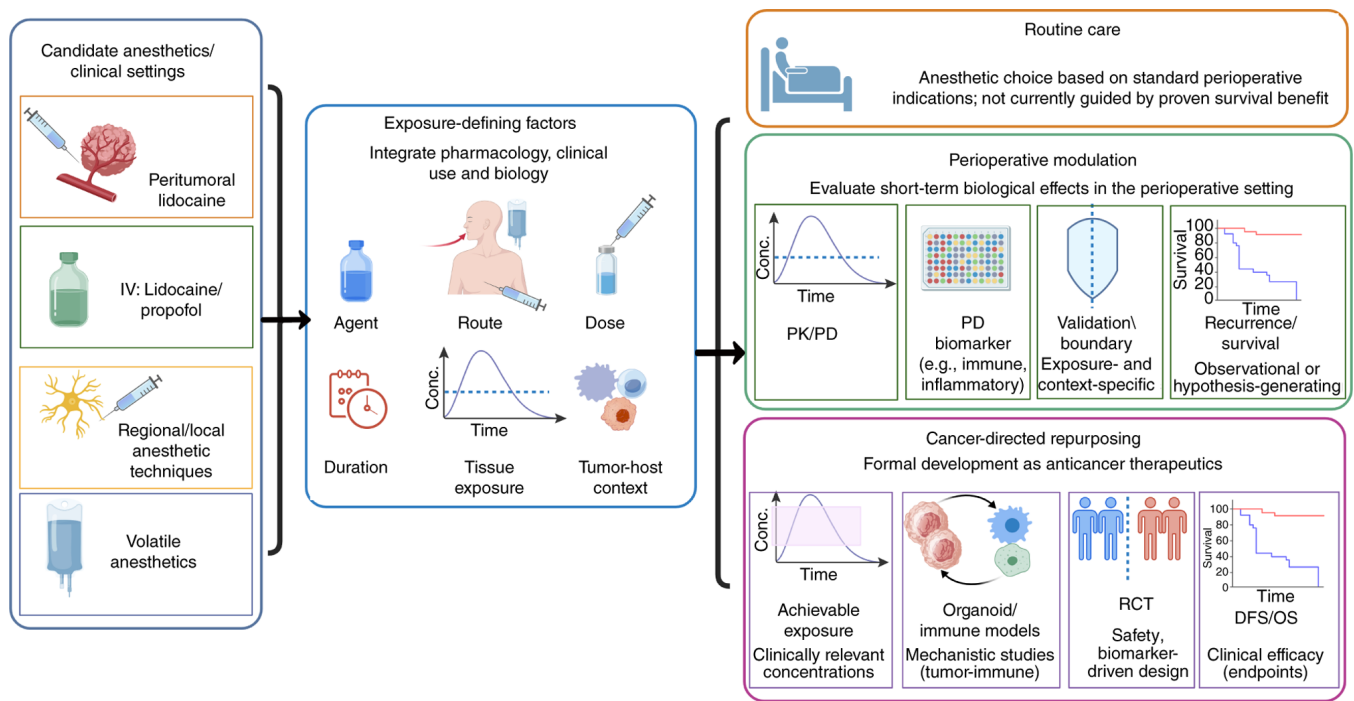


Figure 4. Translational framework for anesthetic-related biological observations in clinical oncology. The framework distinguishes routine anesthetic care, perioperative pharmacological modulation and cancer-directed repurposing according to agent, route, dose, duration, tissue exposure and tumor-host context. Perioperative modulation relies on PK/PD assessment and pharmacodynamic biomarkers, which are not validated surrogates for recurrence or survival. Cancer-directed repurposing additionally requires clinically achievable exposure, mechanistic support, safety evaluation and randomized assessment using clinically meaningful endpoints. DFS, disease-free survival; IV, intravenous; OS, overall survival; PD, pharmacodynamic; PK, pharmacokinetic; RCT, randomized controlled trial.

applications are pursued, both the exposure strategy and the biological rationale will need to extend beyond a simple comparison of standard maintenance anesthetics (15,28). Major perioperative covariates should also be characterized prospectively (16,112). Opioid exposure, regional techniques, transfusion, corticosteroid use, hemodynamic management, surgical complexity and subsequent oncological therapy can all influence inflammatory or immune biology and may modify long-term cancer outcomes (16,21,28). Capturing these variables in advance allows any pharmacodynamic or clinical signal to be interpreted within the perioperative context in which it emerged (112).

Biomarkers, sampling windows and patient stratification. Biomarker interpretation depends as much on timing and biological purpose as on the marker itself. Pathway-specific tissue responses, immune-cell phenotyping and cytokine profiles can indicate whether an intervention has engaged the intended biological process. Circulating tumor DNA (ctDNA) and circulating tumor cells provide information more closely related to tumor burden and minimal residual disease, but neither is inherently specific to anesthetic pharmacology (113-115). Timing is particularly important for ctDNA. Surgical trauma can substantially increase non-tumor cell-free DNA, temporarily reducing the analytical sensitivity of ctDNA detection (116). Samples collected before surgery, immediately after resection, during early recovery and later in the minimal-residual-disease period therefore address different biological questions. A single postoperative measurement can be difficult to interpret without this temporal context.

Patient stratification may be equally important. If anesthetic-related effects depend on tumor genotype, immune state, receptor expression, hypoxia or other microenvironmental features, a modest population-level signal could conceal a larger effect within a biologically defined subgroup. In this setting, biomarkers are most useful when they demonstrate pharmacodynamic activity or enrich for responsive biology. Their use as substitutes for recurrence or survival requires prospective validation for the specific intervention being studied.

Combination strategies. Combination strategies are most defensible when a perioperative agent enhances a defined, established anticancer mechanism at a feasible exposure. Preclinical evidence that local anesthetics can interact with antitumor immunity provides a rationale for studying combinations with immune-checkpoint blockade or targeted delivery approaches (69,117). The critical question is not whether an interaction can be produced *in vitro*, but whether it persists in immune-competent systems and can be demonstrated in patients using the intended route and schedule. Clinical development of a combination requires evidence of the intended biological interaction at an achievable exposure, acceptable safety and a patient population in which the mechanism is relevant. The same standard should apply when cancer-related endpoints are incorporated into studies of multimodal analgesia, attenuation of surgical stress or transfusion optimization. These interventions retain their established perioperative indications; any additional cancer-related benefit must be demonstrated prospectively.

9. Conclusions

Anesthetic-related drugs can modulate tumor-cell and host biology, but the direction and clinical relevance of these effects depend strongly on the agent, route, exposure, tumor type and biological context. Mechanistic and perioperative biomarker findings should therefore not be equated with durable oncological benefit. Current randomized evidence does not support selecting anesthetic techniques solely to improve cancer outcomes. The favorable survival signal observed with preoperative peritumoral lidocaine remains intervention-specific and requires independent confirmation, whereas propofol-based anesthesia has not demonstrated a long-term advantage over volatile anesthesia. Routine anesthetic management should thus remain guided by established perioperative indications. Future translation should focus on clinically achievable exposures linked to defined tumor- or host-specific mechanisms, biologically relevant patient populations and prospectively specified pharmacodynamic and oncological endpoints. Adequately powered randomized trials are required to establish whether selected anesthetic-related agents can serve as reproducible anticancer adjuncts.

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Authors' contributions

TY and JT conceived the review and prepared the initial draft of the manuscript, including the figures and tables. MSM and HH assisted with literature retrieval and manuscript revision. CP and QF provided overall supervision and critically reviewed and edited the manuscript. CP acquired funding and contributed to figure and table editing. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Horowitz M, Neeman E, Sharon E and Ben-Eliyahu S: Exploiting the critical perioperative period to improve long-term cancer outcomes. *Nat Rev Clin Oncol* 12: 213-226, 2015.
- Cheng X, Zhang H, Hamad A, Huang H and Tsung A: Surgery-mediated tumor-promoting effects on the immune microenvironment. *Semin Cancer Biol* 86: 408-419, 2022.
- Bezu L, Akçal Öksüz D, Bell M, Buggy D, Diaz-Cambronero O, Enlund M, Forget P, Gupta A, Hollmann MW, Ionescu D, *et al*: Perioperative immunosuppressive factors during cancer surgery: An updated review. *Cancers (Basel)* 16: 2304, 2024.
- Yang F, Hua Q, Zhu X and Xu P: Surgical stress induced tumor immune suppressive environment. *Carcinogenesis* 45: 185-198, 2024.
- Kim R: Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. *J Transl Med* 16: 8, 2018.
- Onuma AE, Zhang H, Gil L, Huang H and Tsung A: Surgical stress promotes tumor progression: A focus on the impact of the immune response. *J Clin Med* 9: 4096, 2020.
- Ramly MS and Buggy DJ: Anesthetic techniques and cancer outcomes: what is the current evidence? *Anesth Analg* 140: 768-777, 2025.
- Brogi E and Forfori F: Anesthesia and cancer recurrence: An overview. *J Anesth Analg Crit Care* 2: 33, 2022.
- Xia SH, Zhou D, Ge F, Sun M, Chen X, Zhang H and Miao C: Influence of perioperative anesthesia on cancer recurrence: from basic science to clinical practice. *Curr Oncol Rep* 25: 63-81, 2023.
- Choi H and Hwang W: Anesthetic approaches and their impact on cancer recurrence and metastasis: A comprehensive review. *Cancers (Basel)* 16: 4269, 2024.
- Santander Ballestín S, Lanuza Bardaji A, Marco Continente C and Luesma Bartolomé MJ: Antitumor anesthetic strategy in the perioperative period of the oncological patient: A review. *Front Med (Lausanne)* 9: 799355, 2022.
- Wu J, Yang J and Duan J: Anesthetic agents as therapeutic tools in breast cancer: Insights into cancer progression and recurrence. *Clin Breast Cancer* 25: e561-e576, 2025.
- 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* 394: 1807-1815, 2019.
- Cao SJ, Zhang Y, Zhang YX, Zhao W, Pan LH, Sun XD, Jia Z, Ouyang W, Ye QS, Zhang FX, *et al*: Long-term survival in older patients given propofol or sevoflurane anaesthesia for major cancer surgery: Follow-up of a multicentre randomised trial. *Br J Anaesth* 131: 266-275, 2023.
- Bennett-Guerrero E, Romeiser JL, DeMaria S, Nadler JW, Quinn TD, Ponnappan SK, Wang R, Gloff MS, Lee KJ, Levin MA, *et al*: Anesthesia type during cancer surgery: Results of the GA-CARES randomized, multicenter trial. *Anesthesiology* 144: 51-62, 2026.
- Hiller JG, Perry NJ, Poulogiannis G, Riedel B and Sloan EK: Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol* 15: 205-218, 2018.
- Reysner T and Reysner M: Regional anesthesia and the perioperative inflammatory window in cancer surgery: From surgical stress to immunometabolic reprogramming. *Cancers (Basel)* 18: 1158, 2026.
- Reysner T, Wiczerowska-Tobis K, Kowalski G, Grochowicka M, Pyszczorska M, Mularski A and Reysner M: The influence of regional anesthesia on the systemic stress response. *Reports* 7: 89, 2024.
- Wall TP and Buggy DJ: Perioperative intravenous lidocaine and metastatic cancer recurrence-A narrative review. *Front Oncol* 11: 688896, 2021.
- Sahinovic MM, Struys MMR and Absalom AR: Clinical pharmacokinetics and pharmacodynamics of propofol. *Clin Pharmacokinet* 57: 1539-1558, 2018.
- Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW and Hollmann MW: Perioperative anesthesia care and tumor progression. *Anesth Analg* 124: 1697-1708, 2017.

22. Zhou X, Shao Y, Li S, Zhang S, Ding C, Zhuang L and Sun J: An intravenous anesthetic drug-propofol, influences the biological characteristics of malignant tumors and reshapes the tumor microenvironment: A narrative literature review. *Front Pharmacol* 13: 1057571, 2022.
23. Piegeler T, Schl pfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD and Beck-Schimmer B: Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNF α -induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. *Br J Anaesth* 115: 784-791, 2015.
24. Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P and Akladios C: Antitumor effects of lidocaine on human breast cancer cells: An in vitro and in vivo experimental trial. *Anticancer Res* 38: 95-105, 2018.
25. Zhou R, Konishi Y, Zhang A and Nishiaki K: Propofol elicits apoptosis and attenuates cell growth in esophageal cancer cell lines. *Nagoya J Med Sci* 85: 579-591, 2023.
26. Lai RC, Shan WR, Zhou D, Zeng XQ, Zuo K, Pan DF, Zeng WA and Zuo ZY: Sevoflurane promotes migration, invasion, and colony-forming ability of human glioblastoma cells possibly via increasing the expression of cell surface protein 44. *Acta Pharmacol Sin* 40: 1424-1435, 2019.
27. Chamaraux-Tran TN and Piegeler T: The amide local anesthetic lidocaine in cancer surgery-potential antimetastatic effects and preservation of immune cell function? A narrative review. *Front Med (Lausanne)* 4: 235, 2017.
28. Murphy L, Shaker J and Buggy DJ: Anaesthetic techniques and strategies: Do they influence oncological outcomes? *Curr Oncol* 30: 5309-5321, 2023.
29. D'Agostino G, Saporito A, Cecchinato V, Silvestri Y, Borgeat A, Anselmi L and Uguccioni M: Lidocaine inhibits cytoskeletal remodelling and human breast cancer cell migration. *Br J Anaesth* 121: 962-968, 2018.
30. Liu H, Dilger JP and Lin J: Lidocaine suppresses viability and migration of human breast cancer cells: TRPM7 as a target for some breast cancer cell lines. *Cancers (Basel)* 13: 234, 2021.
31. Liu C, Yu M, Li Y, Wang H, Xu C, Zhang X, Li M, Guo H, Ma D and 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* 10: 337-349, 2021.
32. Rizaner N, Fraser SP, Gul IB, Purut E, Djamgoz MBA and Altun S: Lidocaine inhibits rat prostate cancer cell invasiveness and voltage-gated sodium channel expression in plasma membrane. *J Membr Biol* 257: 17-24, 2024.
33. Djamgoz MBA, Fraser SP and Brackenbury WJ: In vivo evidence for voltage-gated sodium channel expression in carcinomas and potentiation of metastasis. *Cancers (Basel)* 11: 1675, 2019.
34. Wall TP, Crowley PD, Sherwin A, Foley AG and Buggy DJ: Effects of lidocaine and Src inhibition on metastasis in a murine model of breast cancer surgery. *Cancers (Basel)* 11: 1414, 2019.
35. Patel A, Sabbineni H, Clarke A and Somanath PR: Novel roles of Src in cancer cell epithelial-to-mesenchymal transition, vascular permeability, microinvasion and metastasis. *Life Sci* 157: 52-61, 2016.
36. Lirk P, Berger R, Hollmann MW and Fiegl H: Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. *Br J Anaesth* 109: 200-207, 2012.
37. Li K, Yang J and Han X: Lidocaine sensitizes the cytotoxicity of cisplatin in breast cancer cells via up-regulation of RAR β 2 and RASSF1A demethylation. *Int J Mol Sci* 15: 23519-23536, 2014.
38. Hsieh WH, Liao SW, Chan SM, Hou JD, Wu SY, Ho BY, Chen KY, Tai YT, Fang HW, Fang CY, *et al.*: Lidocaine induces epithelial-mesenchymal transition and aggravates cancer behaviors in non-small cell lung cancer A549 cells. *Oncol Lett* 26: 346, 2023.
39. Xing B, Yang L and Cui Y: Lidocaine inhibited migration of NSCLCA549 cells via the CXCR4 regulation. *Cancer Biomark* 33: 317-330, 2022.
40. Li R, Xiao C, Liu H, Huang Y, Dilger JP and Lin J: Effects of local anesthetics on breast cancer cell viability and migration. *BMC Cancer* 18: 666, 2018.
41. Jiang S, Liu Y, Huang L, Zhang F and Kang R: Effects of propofol on cancer development and chemotherapy: Potential mechanisms. *Eur J Pharmacol* 831: 46-51, 2018.
42. Buschmann D, Brandes F, Lindemann A, Maerte M, Ganschow P, Chouker A, Schelling G, Pfaffl MW and Reithmair M: Propofol and sevoflurane differentially impact MicroRNAs in circulating extracellular vesicles during colorectal cancer resection: A pilot study. *Anesthesiology* 132: 107-120, 2020.
43. Chang Q, Wu J, An Y, Liu H and Sun Y: Propofol suppresses proliferation, migration, invasion, and tumor growth of liver cancer cells via suppressing cancer susceptibility candidate 9/phosphatase and tensin homolog/AKT serine/threonine kinase/mechanistic target of rapamycin kinase axis. *Hum Exp Toxicol* 41: 9603271211065972, 2022.
44. Wang R, Li S, Hou Q, Zhang B, Chu H, Hou Y, Ni C, Sun L, Ran Y and Zheng H: Propofol inhibits colon cancer cell stemness and epithelial-mesenchymal transition by regulating SIRT1, Wnt/ β -catenin and PI3K/AKT/mTOR signaling pathways. *Discov Oncol* 14: 137, 2023.
45. Wang Y, Xu B, Zhou J and Wu X: Propofol activates AMPK to inhibit the growth of HepG2 cells in vitro and hepatocarcinogenesis in xenograft mouse tumor models by inducing autophagy. *J Gastrointest Oncol* 11: 1322-1332, 2020.
46. Sun L, Ma W, Gao W, Xing Y, Chen L, Xia Z, Zhang Z and Dai Z: Propofol directly induces caspase-1-dependent macrophage pyroptosis through the NLRP3-ASC inflammasome. *Cell Death Dis* 10: 542, 2019.
47. Wang Z, Cao B, Ji P and Yao F: Propofol inhibits tumor angiogenesis through targeting VEGF/VEGFR and mTOR/eIF4E signaling. *Biochem Biophys Res Commun* 555: 13-18, 2021.
48. Yang N, Liang Y, Yang P and Ji F: Propofol suppresses LPS-induced nuclear accumulation of HIF-1 α and tumor aggressiveness in non-small cell lung cancer. *Oncol Rep* 37: 2611-2619, 2017.
49. Schito L and Semenza GL: Hypoxia-inducible factors: Master regulators of cancer progression. *Trends Cancer* 2: 758-770, 2016.
50. Lu H, Zheng G, Gao X, Chen C, Zhou M and Zhang L: Propofol suppresses cell viability, cell cycle progression and motility and induces cell apoptosis of ovarian cancer cells through suppressing MEK/ERK signaling via targeting circVPS13C/miR-145 axis. *J Ovarian Res* 14: 30, 2021.
51. Shen X, Wang D, Chen X and Peng J: Propofol inhibits proliferation, migration, invasion and promotes apoptosis by regulating HOST2/JAK2/STAT3 signaling pathway in ovarian cancer cells. *Cytotechnology* 73: 243-252, 2021.
52. Gao M, Guo R, Lu X, Xu G and Luo S: Propofol suppresses hypoxia-induced esophageal cancer cell migration, invasion, and EMT through regulating lncRNA TMPO-AS1/miR-498 axis. *Thorac Cancer* 11: 2398-2405, 2020.
53. Fan X, Gong M, Yu H, Yang H, Wang S and Wang R: Propofol enhances stem-like properties of glioma via GABA $_A$ -dependent Src modulation of ZDHHC5-EZH2 palmitoylation mechanism. *Stem Cell Res Ther* 13: 398, 2022.
54. Benzonana LL, Perry NJS, Watts HR, Yang B, Perry IA, Coombes C, Takata M and Ma D: Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia-inducible factor cellular signaling pathway in vitro. *Anesthesiology* 119: 593-605, 2013.
55. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, Brown R and Ma D: Prostate cancer cell malignancy via modulation of HIF-1 α pathway with isoflurane and propofol alone and in combination. *Br J Cancer* 111: 1338-1349, 2014.
56. Ishikawa M, Iwasaki M, Zhao H, Saito J, Hu C, Sun Q, Sakamoto A and Ma D: Inhalational anesthetics inhibit neuro-glioma cell proliferation and migration via miR-138, -210 and -335. *Int J Mol Sci* 22: 4355, 2021.
57. Zhao H, Xing F, Yuan J, Li Z and Zhang W: Sevoflurane inhibits migration and invasion of glioma cells via regulating miR-34a-5p/MMP-2 axis. *Life Sci* 256: 117897, 2020.
58. Scroope CA, Singleton Z, Hollmann MW and Parat MO: Opioid receptor-mediated and non-opioid receptor-mediated roles of opioids in tumour growth and metastasis. *Front Oncol* 11: 792290, 2021.
59. Zhou Y, Li W, Chen Y, Hu X and Miao C: Research progress on the impact of opioids on the tumor immune microenvironment (review). *Mol Clin Oncol* 22: 53, 2025.
60. Wang Z, Jiang L, Wang J, Chai Z and Xiong W: Morphine promotes angiogenesis by activating PI3K/Akt/HIF-1 α pathway and upregulating VEGF in hepatocellular carcinoma. *J Gastrointest Oncol* 12: 1761-1772, 2021.
61. Zhang H, Zhou D, Gu J, Qu M, Guo K, Chen W and Miao C: Targeting the mu-opioid receptor for cancer treatment. *Curr Oncol Rep* 23: 111, 2021.
62. Ramirez MF, Strang A, Roland G, Lasala J and Owusu-Agyemang P: Perioperative pain management and cancer outcomes: A narrative review. *J Pain Res* 16: 4181-4189, 2023.

63. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G and Ma D: Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: Systematic review and meta-analysis. *Br J Anaesth* 123: 777-794, 2019.
64. Yuki K: The immunomodulatory mechanism of dexmedetomidine. *Int Immunopharmacol* 97: 107709, 2021.
65. Jun JH, Shim JK, Oh JE, Kim KS, Kwak YL and Soh S: Effects of dexmedetomidine on A549 non-small cell lung cancer growth in a clinically relevant surgical xenograft model. *Sci Rep* 13: 12471, 2023.
66. Zhang C, Qu Y, Cao Q, Tao Y, Huai X, Xuan W, Pan Z, Wang X and Tian J: Effect of intraoperative dexmedetomidine on prognosis in patients with cancer undergoing surgical procedures: A systematic review and meta-analysis. *Br J Anaesth* 135: 89-98, 2025.
67. Bied M, Ho WW, Ginhoux F and Blériot C: Roles of macrophages in tumor development: A spatiotemporal perspective. *Cell Mol Immunol* 20: 983-992, 2023.
68. Yaniv D, Mattson B, Talbot S, Gleber-Netto FO and Amit M: Targeting the peripheral neural-tumour microenvironment for cancer therapy. *Nat Rev Drug Discov* 23: 780-796, 2024.
69. 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 Immunother Cancer* 10: e004151, 2022.
70. Ramirez MF, Tran P and Cata JP: The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. *Reg Anesth Pain Med* 40: 43-48, 2015.
71. Cata JP, Ramirez MF, Velasquez JF, Di AI, Popat KU, Gottumukkala V, Black DM, Lewis VO and Vauthey JN: Lidocaine stimulates the function of natural killer cells in different experimental settings. *Anticancer Res* 37: 4727-4732, 2017.
72. Wu YY, Chen MS, Chen IC, Wu FH, Liao TL, Wen HW, Nielsen BL and Liu HJ: Lidocaine modulates cytokine production and reprograms the tumor immune microenvironment to enhance anti-tumor immune responses in gastric cancer. *Int J Mol Sci* 26: 3236, 2025.
73. Lim JA, Oh CS, Yoon TG, Lee JY, Lee SH, Yoo YB, Yang JH and Kim SH: The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: An in vitro analysis. *BMC Cancer* 18: 159, 2018.
74. Buckley A, McQuaid S, Johnson P and Buggy DJ: Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. *Br J Anaesth* 113 (Suppl 1): i56-i62, 2014.
75. Apisutimaitri K, Saeyup P, Suppipat K, Sirichindakul P, Wanarisant N, Nonsri C and Lertprapai P: Effects of propofol-based total intravenous anesthesia versus desflurane anesthesia on natural killer cell cytotoxicity after hepatocellular carcinoma resection. *J Anaesthesiol Clin Pharmacol* 40: 395-402, 2024.
76. Gao J, Hu H and Wang X: Clinically relevant concentrations of lidocaine inhibit tumor angiogenesis through suppressing VEGF/VEGFR2 signaling. *Cancer Chemother Pharmacol* 83: 1007-1015, 2019.
77. Cole SW and Sood AK: Molecular pathways: Beta-adrenergic signaling in cancer. *Clin Cancer Res* 18: 1201-1206, 2012.
78. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, Jennings NB, Armaiz-Pena G, Bankson JA, Ravoori M, *et al*: Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med* 12: 939-944, 2006.
79. Sloan EK, Priceman SJ, Cox BF, Yu S, Pimentel MA, Tangkanangkul V, Arevalo JM, Morizono K, Karanikolas BD, Wu L, *et al*: The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res* 70: 7042-7052, 2010.
80. Haldar R, Ricon-Becker I, Radin A, Gutman M, Cole SW, Zmora O and Ben-Eliyahu S: Perioperative COX2 and β -adrenergic blockade improves biomarkers of tumor metastasis, immunity, and inflammation in colorectal cancer: A randomized controlled trial. *Cancer* 126: 3991-4001, 2020.
81. Shaashua L, Shabat-Simon M, Haldar R, Matzner P, Zmora O, Shabtai M, Sharon E, Allweis T, Barshack I, Hayman L, *et al*: Perioperative COX-2 and β -adrenergic blockade improves metastatic biomarkers in breast cancer patients in a phase-II randomized trial. *Clin Cancer Res* 23: 4651-4661, 2017.
82. Haldar R, Shaashua L, Lavon H, Lyons YA, Zmora O, Sharon E, Birnbaum Y, Allweis T, Sood AK, Barshack I, *et al*: Perioperative inhibition of β -adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. *Brain Behav Immun* 73: 294-309, 2018.
83. Ripollés-Melchor J, Abad-Motos A and Zorrilla-Vaca A: Enhanced recovery after surgery (ERAS) in surgical oncology. *Curr Oncol Rep* 24: 1177-1187, 2022.
84. Lee ZX, Ng KT, Ang E, Wang CY and Binti Shariffuddin IIB: Effect of perioperative regional anesthesia on cancer recurrence: A meta-analysis of randomized controlled trials. *Int J Surg* 82: 192-199, 2020.
85. 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* 41: 3318-3328, 2023.
86. Zheng Q, Peng X and 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* 20: 43, 2020.
87. Xu P, Zhang S, Tan L, Wang L, Yang Z and Li J: Local anesthetic ropivacaine exhibits therapeutic effects in cancers. *Front Oncol* 12: 836882, 2022.
88. Xuan W, Zhao H, Hankin J, Chen L, Yao S and Ma D: Local anesthetic bupivacaine induced ovarian and prostate cancer apoptotic cell death and underlying mechanisms in vitro. *Sci Rep* 6: 26277, 2016.
89. Wang S, Li M, Cai S and Zhang W: Transcriptome analysis reveals the differential inflammatory effects between propofol and sevoflurane during lung cancer resection: A randomized pilot study. *World J Surg Oncol* 21: 8, 2023.
90. Li Y, Sun L, Zhou Q, Lee AJ, Wang L, Zhang R and Wang S: Effects of opioid drugs on immune function in cancer patients. *Biomed Pharmacother* 175: 116665, 2024.
91. Klein JA and Jeske DR: Estimated maximal safe dosages of tumescent lidocaine. *Anesth Analg* 122: 1350-1359, 2016.
92. Toner AJ, Bailey MA, Schug SA and Corcoran TB: A pilot multicentre randomised controlled trial of lidocaine infusion in women undergoing breast cancer surgery. *Anaesthesia* 76: 1326-1341, 2021.
93. Toner AJ, Bailey MA, Schug SA, Phillips M, Ungerer JPI, Somogyi AA and Corcoran TB: Serum lidocaine (lignocaine) concentrations during prolonged perioperative infusion in patients undergoing breast cancer surgery: A secondary analysis of a randomised controlled trial. *Anaesth Intensive Care* 51: 422-431, 2023.
94. Greenwood E, Nimmo S, Paterson H, Homer N and Foo I: Intravenous lidocaine infusion as a component of multimodal analgesia for colorectal surgery-measurement of plasma levels. *Perioper Med (Lond)* 8: 1, 2019.
95. Chhabra D, Bhatia P, Sethi P, Kalaria N, Kumar M and Kaur M: To ascertain the plasma concentration of propofol to achieve bispectral index-guided sedation using a target-controlled infusion in patients undergoing elective surgeries under neuraxial anaesthesia. *Indian J Anaesth* 66: 832-836, 2022.
96. Mazoit JX and Samii K: Binding of propofol to blood components: Implications for pharmacokinetics and for pharmacodynamics. *Br J Clin Pharmacol* 47: 35-42, 1999.
97. Colonna G: Overcoming barriers in cancer biology research: Current limitations and solutions. *Cancers (Basel)* 17: 2102, 2025.
98. Olson B, Li Y, Lin Y, Liu ET and Patnaik A: Mouse models for cancer immunotherapy research. *Cancer Discov* 8: 1358-1365, 2018.
99. Yang Y, Cui J, Kong Y, Hou Y and Ma C: Organoids: New frontiers in tumor immune microenvironment research. *Front Immunol* 15: 1422031, 2024.
100. Tang Y, Tang L, Yao Y, Huang H and Chen B: Effects of anesthesia on long-term survival in cancer surgery: A systematic review and meta-analysis. *Heliyon* 10: e24791, 2024.
101. Polak R, Zhang ET and Kuo CJ: Cancer organoids 2.0: Modelling the complexity of the tumour immune microenvironment. *Nat Rev Cancer* 24: 523-539, 2024.
102. Yang R and Yu Y: Patient-derived organoids in translational oncology and drug screening. *Cancer Lett* 562: 216180, 2023.
103. Wang D, Villenave R, Stokar-Regenscheit N and Clevers H: Human organoids as 3D in vitro platforms for drug discovery: Opportunities and challenges. *Nat Rev Drug Discov* 25: 204-226, 2026.

104. Liu X, Fang J, Huang S, Wu X, Xie X, Wang J, Liu F, Zhang M, Peng Z and Hu N: Tumor-on-a-chip: From bioinspired design to biomedical application. *Microsyst Nanoeng* 7: 50, 2021.
105. Ayuso JM, Rehman S, Virumbrales-Munoz M, McMinn PH, Geiger P, Fitzgerald C, Heaster T, Skala MC and Beebe DJ: Microfluidic tumor-on-a-chip model to evaluate the role of tumor environmental stress on NK cell exhaustion. *Sci Adv* 7: eabc2331, 2021.
106. Xiao J, Yu X, Meng F, Zhang Y, Zhou W, Ren Y, Li J, Sun Y, Sun H, Chen G, *et al*: Integrating spatial and single-cell transcriptomics reveals tumor heterogeneity and intercellular networks in colorectal cancer. *Cell Death Dis* 15: 326, 2024.
107. Jin Y, Zuo Y, Li G, Liu W, Pan Y, Fan T, Fu X, Yao X and Peng Y: Advances in spatial transcriptomics and its applications in cancer research. *Mol Cancer* 23: 129, 2024.
108. Janesick A, Shelansky R, Gottscho AD, Wagner F, Williams SR, Rouault M, Beliakoff G, Morrison CA, Oliveira MF, Sicherman JT, *et al*: High resolution mapping of the tumor microenvironment using integrated single-cell, spatial and in situ analysis. *Nat Commun* 14: 8353, 2023.
109. Du Y, Shi J, Wang J, Xun Z, Yu Z, Sun H, Bao R, Zheng J, Li Z and Ye Y: Integration of pan-cancer single-cell and spatial transcriptomics reveals stromal cell features and therapeutic targets in tumor microenvironment. *Cancer Res* 84: 192-210, 2024.
110. Lei W, Zhou K, Lei Y, Li Q and Zhu H: Gut microbiota shapes cancer immunotherapy responses. *NPJ Biofilms Microbiomes* 11: 143, 2025.
111. Jiang N, Wang L, Chen X and Yu C: Interactions between perioperative anesthesia management and gut microbiota: Current research advances. *Cell Mol Neurobiol* 46: 67, 2026.
112. Bell M, Buggy DJ, Brattström D, Buchli C, Debouche S, Granath F, Riedel B and Gupta A: The effects of anaesthesia and analgesia on short- and long-term outcomes following colorectal cancer surgery: Protocol for an international, pragmatic, cohort study (ENCORE). *Eur J Anaesthesiol Intensive Care* 3: e0051, 2024.
113. Huang Q, Zhou R, Hao X, Zhang W, Chen G and Zhu T: Circulating biomarkers in perioperative management of cancer patients. *Precis Clin Med* 6: pbad018, 2023.
114. Efthymiou V, Queenan N, Haas M, Naegele S, Goss D and Faden DL: Circulating tumor DNA in the immediate postoperative setting. *Ann Surg Oncol* 31: 2319-2325, 2024.
115. Dai CS, Mishra A, Edd J, Toner M, Maheswaran S and Haber DA: Circulating tumor cells: Blood-based detection, molecular biology, and clinical applications. *Cancer Cell* 43: 1399-1422, 2025.
116. Henriksen TV, Reinert T, Christensen E, Sethi H, Birkenkamp-Demtröder K, Gögenur M, Gögenur I, Zimmermann BG, IMPROVE Study Group, Dyrskjøl L and Andersen CL: The effect of surgical trauma on circulating free DNA levels in cancer patients-implications for studies of circulating tumor DNA. *Mol Oncol* 14: 1670-1679, 2020.
117. Bezu L, Kepp O and Kroemer G: Local anesthetics and immunotherapy: A novel combination to fight cancer. *Semin Immunopathol* 45: 265-272, 2023.



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