animals

MDPI

Review

Anaesthesia in Veterinary Oncology: The Effects of Surgery, Volatile and Intravenous Anaesthetics on the Immune System and Tumour Spread

Ana Vidal Pinheiro [1,*], Gonçalo N. Petrucci [2,3,4], Amândio Dourado [1,2] and Isabel Pires [1,4]

[1] Department of Veterinary Sciences, School of Agricultural and Veterinary Sciences (ECAV), University of Trás-os-Montes e Alto Douro (UTAD), 5000-801 Vila Real, Portugal; amandio.dourado@onevetgroup.pt (A.D.); ipires@utad.pt (I.P.)
[2] Onevetgroup Hospital Veterinário do Porto (HVP), 4250-475 Porto, Portugal; goncalopetrucci@gmail.com
[3] Center for Investigation Vasco da Gama (CIVG), Department of Veterinary Sciences, Vasco da Gama University School (EUVG), 3020-210 Coimbra, Portugal
[4] CECAV—Veterinary and Animal Research Center, University of Trás-os-Montes and Alto Douro, 5001-801 Vila Real, Portugal
* Correspondence: acvpvidal@gmail.com

Simple Summary: Anaesthesia plays an important role in diagnosis procedures and the treatment and pain management of oncological patients. However, studies suggest that anaesthetic drugs may increase the risk of tumour dissemination in the perioperative period by directly and indirectly suppressing the immune system, which is primarily responsible for controlling tumour growth. Science faces the challenge of understanding their influence on the immune system to develop anaesthetic strategies that assure greater immune stability in patients with cancer or other immune-compromising diseases.

Abstract: Throughout the course of oncological disease, the majority of patients require surgical, anaesthetic and analgesic intervention. However, during the perioperative period, anaesthetic agents and techniques, surgical tissue trauma, adjuvant drugs for local pain and inflammation and other non-pharmacological factors, such as blood transfusions, hydration, temperature and nutrition, may influence the prognosis of the disease. These factors significantly impact the oncologic patient's immune response, which is the primary barrier to tumour progress, promoting a window of vulnerability for its dissemination and recurrence. More research is required to ascertain which anaesthetics and techniques have immunoprotective and anti-tumour effects, which will contribute to developing novel anaesthetic strategies in veterinary medicine.

Keywords: perioperative period; surgery; immune system; tumours; intravenous anaesthetics; volatile anaesthetics; veterinary oncology

check for updates

Citation: Pinheiro, A.V.; Petrucci, G.N.; Dourado, A.; Pires, I. Anaesthesia in Veterinary Oncology: The Effects of Surgery, Volatile and Intravenous Anaesthetics on the Immune System and Tumour Spread. *Animals* **2023**, *13*, 3392. https://doi.org/10.3390/ani13213392

Academic Editor: Cinzia Benazzi

Received: 16 September 2023
Revised: 11 October 2023
Accepted: 30 October 2023
Published: 1 November 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The growing attention paid to animal health [1] and the development of novel diagnostic and therapeutic procedures have significantly impacted the lifespan of companion animals [2]. Malignant tumours tend to be more prevalent in older animals [3,4], which can be linked to various age-related factors such as alterations in cell-mediated immunity and the phenomenon of immunosenescence [5]. The diagnosis of cancer in dogs and cats has increased significantly in recent years, making it one of the most prevalent causes of death. [6,7]. This fact has led to novel therapeutic oncology approaches, which are considered based on the tumour line and the patient's health [8]. Surgical excision is still considered the gold standard for treating solid tumours [9]; however, even in tumour resections with histologically clean margins, an undetected residual risk of the intra-surgical dissemination of tumour cells still exists [10]. For this reason, it is often required to combine

surgical excision with other treatment alternatives, such as chemotherapy, radiation or biological therapies [11–14].

Considering human and animal studies, the main risk of tumour dissemination occurs in the perioperative period [15,16], during which cancer cells and the immune system are influenced by stress, pain [17,18], anaesthesia [19] and surgical procedures [20]. These factors induce a stress response that starts a cascade of physiological mechanisms beneficial to the restoration of homeostasis but also favourable to tumour growth [20], which include immunomodulatory and pro-tumour effects such as immune suppression and tumour angiogenesis [17,18]. Therefore, the perioperative period can be seen as a window of opportunity to minimise the pro-tumour and anti-immune mechanisms triggered by surgical stress and anaesthetic drugs, suggesting new clinical approaches with neurophysiological and immune preservation. Alternative surgical and anaesthetic procedures, such as minimally invasive surgery [21], regional anaesthesia [22], opioid-free anaesthesia [23], total intravenous anaesthesia [24] and multimodal analgesia [25,26], are gaining significance in clinical practice, with particular emphasis on oncological patients due to their immunoprotective effects.

According to this knowledge, this review aims to debate the influence of anaesthetic drugs on the immune system and tumour cells based on retrospective studies in humans and animals.

2. Search Methodology

This review has been conducted to describe the outcomes of relevant experimental studies. A search strategy of the PubMed database was conducted to find the qualifying articles. We applied the following keywords: "anaesthetic strategies in oncological surgery"; "anaesthesia and cancer"; "anaesthesia and cancer recurrence and metastasis"; "veterinary anaesthesia oncology"; "cancer in anaesthesia dogs"; "anaesthesia and cancer recurrence and metastasis in dogs"; "regional anaesthesia in animals"; "total intravenous anaesthesia in small animals"; "intravenous anaesthetics and tumour spread"; "volatile anaesthetics and tumour spread"; "surgery and immune system"; "surgery and tumour dissemination"; "perioperative period and tumour spread"; "cancer and immune system". The search terms determined were full text, ten years, randomised controlled trial, clinical trial, meta-analysis, review and veterinary anaesthesia.

3. The Immune System as the Main Player in the Tumour's Defence

The tumour growth and spread process is influenced by the tumour's characteristics but mainly by the host's immune system [8]. The scientific community recognises that a high number and high activity of natural killer cells and cytotoxic T lymphocytes correlate with enhanced anti-tumour immune responses and the elimination of neoplastic cells from blood circulation [27,28]. Likewise, dendritic cells (DCs) are an essential subpopulation of leukocytes for inducing and regulating an adaptive anti-tumour immune response [29]. Cancer immunoediting is part of a dynamic concept that explains the role of the immune system and immune cells in malignant transformation, emphasising cancer immunotherapy [30].

In veterinary and human searches, a high count and ratio of circulating leukocytes (CD4+ and CD8+ T cells, dendritic cells, macrophages and regulatory T cells) [31,32], as well as their presence in the tumour microenvironment [33,34], may be associated with the prognosis of certain solid tumours. In felines with mammary carcinoma, the neutrophil-to-lymphocyte ratio has been suggested as a prognostic factor. In contrast, high numbers of total leukocyte counts, neutrophils, and the neutrophil/lymphocyte ratio were associated with an increased risk of tumour-related death [31]. Moreover, the lymphocyte/monocyte ratio can predict the prognosis of newly diagnosed canines with diffuse large B-cell lymphoma in terms of time progression and lymphoma-specific survival [32] and the histopathological grade of canine mast cell tumours [35]. In canine osteosarcoma, monocyte and lymphocyte counts were used as prognostic indicators [36].

Other studies observed that in dogs with oncological disease, the percentage of Th1 was considerably lower and Th2 was significantly higher compared to healthy dogs [37]. In addition, they determined that dogs with metastases had even lower Th1 values than ill dogs without metastases [37]. Researchers observed a correlation between tumour-infiltrating lymphocytes and histopathological characteristics in canines with mammary carcinoma, suggesting that a significant quantity of lymphocytes infiltrating mammary carcinoma is associated with lymphatic invasion and a high histopathological grade [38]. Furthermore, the tumour-infiltrating lymphocytes proved indispensable for tumour growth and their spread potential [38]. In the review "A role for T-lymphocytes in human breast cancer and in canine mammary tumours", the authors compare tumour T-lymphocyte infiltration and the CD4+/CD8+ T-cell ratio with low survival rates, the action of Th2 cells in the acceleration of tumour progression and a poor prognosis with the presence of large numbers of Treg cells [39]. In human breast cancer, the role of macrophages in tumour progression was observed as a facilitator of the invasion of tumour cells [40] due to their plasticity and ability to adapt to the different physiological conditions that the body presents, which promote the production of cytokines type II, anti-inflammatory responses, and pro-tumour functions [41]. In pancreatic and colorectal human cancers, elevated Th2 levels and an imbalance of the Th1/Th2 ratio lead to an increase in pro-inflammatory interleukins that promote the progression of the disease [42,43].

Considering the immune system as a main player in the body's defence against tumour growth, some human and animal studies suggest a new approach to minimising the impact on the immune cells of several suppressive factors such as stress, pain, anaesthesia and surgery [19,44,45]. According to studies in dogs, the administration of recombinant canine interferon (rCaIFN-γ) before, during and after anaesthesia may reduce the suppression of natural killer (NK) activity, inhibit intraoperative cancer cell dissemination and prevent postoperative cancer recurrence and metastasis [46,47]. In humans, it has been demonstrated that the administration of nonsteroidal anti-inflammatory agents to oncological patients has anti-tumour properties by inhibiting the pro-tumour activity of the enzyme COX-2 of macrophages and increasing the activity of T regulatory cells [48,49], both of which have been shown to promote tumour progression in humans. Dendritic cells also play an important role in immunotherapies, eliciting Th1 and Th17 cell differentiation [50] and infiltrating solid malignancies [51].

4. Tumour Surgery as a "Starting Point" for Tumour Progression

Excisional tumour surgery is the main approach for treating primary solid tumours [9] and the major facilitator of metastatic cell dissemination [52]. Since the eighteenth century, this condition has been researched as a "starting point" for accelerating tumour progression [53]. Since then, several studies have been published on the relationship between surgery and cancer progression to understand this biological behaviour, including 1. the dissemination of tumour cells via the manipulation of the neoplastic tissue [54]; 2. the effect of surgery as a window of opportunity for the development and spread of tumour cells [55]; 3. the change in the state of tumour dormancy via surgical tumour excision [56] and decreased antiangiogenic factor secretion [57].

First, the surgical manipulation of neoplastic tissue promotes the release of neoplastic cells into the blood and lymphatic system [54], where they seek pre-metastatic niches to initiate a new cell growth cycle [58]. Besides that, before surgery, most oncology patients already have cancer cells in their circulatory system, which does not necessarily indicate the presence of metastases or tumour recurrence [59,60]. In human research, less than 0.01% of circulating tumour cells are successful in tumour metastasis, depending on the immune response and the tumour cells' ability to avoid the defence cells [61]. Nonetheless, human investigations have demonstrated a correlation between tumour cells in peripheral blood after surgery and poor prognosis prediction [62].

Secondly, the microenvironment of the damaged tissue in the area of the surgical procedure changes, and minutes after the incision, a proportional local and systemic stress

response is generated [20]. Physiological mechanisms such as local inflammation, sympathetic nervous system activation, and the hypothalamic–pituitary–adrenal axis (HPA) are activated to restore cellular and tissue homeostasis following tissue injury [20], as demonstrated in Figure 1. In response, immunomodulatory chemicals are released, specifically catecholamines and glucocorticoids, which induce prostaglandins (PGE2), pro-inflammatory cytokines (e.g., IL-10), metalloproteinases and endothelial growth factor secretion [17]. These immunomodulatory effects can result in a suppression of the immune system, producing direct and indirect pro-tumour effects such as tumour angiogenesis, the activation of 2-adrenergic and cyclooxygenase-2 receptors, the release of coagulation factors, and the depletion of natural killer cell (lymphocytes CD3- and CD56+) activity [18], which plays a significant role in anti-tumour immunity by controlling the dissemination of cancer cells [27,28]. Platelets and coagulation factors are released to reestablish haemostasis, forming protective aggregates that shield tumour cells from natural killer cells [63]. In actuality, this biological process, which simultaneously attempts to restore homeostasis, modifies the immunological, metabolic, endocrinological, neuronal, inflammatory and immune microenvironments, thereby fostering tumour growth and dissemination [18].

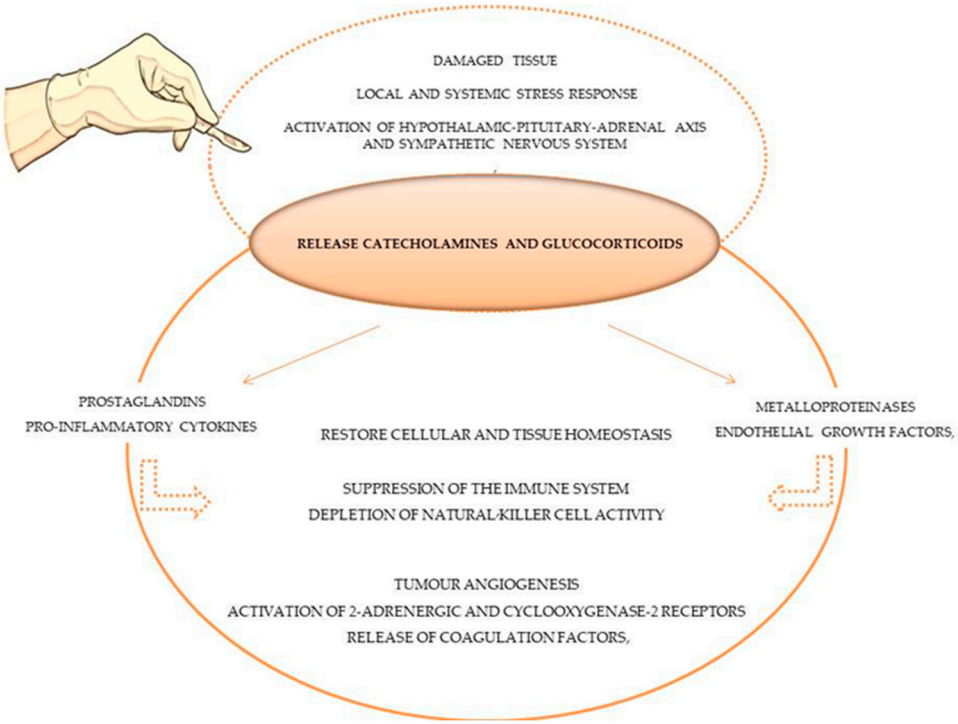


Figure 1. Stress and inflammatory response of tissue surgery damage in immune system and tumour cells.

Considering the inflammatory, immunosuppressive and tumour-spreading effects of surgery trauma, the potential advantages of minimally invasive surgery (MIS) over conventional open surgery have been discussed in human and animal studies, but with inconsistent results [21,64]. MIS seems to offer certain benefits, including reduced tissue inflammation and immune suppression, as well as less blood loss, decreased postoperative pain and reduced hospitalisation [21,64,65]. However, longer surgical and anaesthesia times and an increased risk of technical complications, such as wound dehiscence and local inflammation, could potentially be disadvantages when compared to open surgery [56,66,67].

Lastly, tumour dormancy is a condition characterised by the presence of tumour cells in the absence of evidence of oncological disease [68]. This phenomenon may explain both cancer recurrences after long periods of remission and the maintenance of reduced neoplastic cells after adjuvant oncological therapies [69], as a result of the absence of angiogenic

competence, a homeostatic equilibrium between tumour cells and the immune response or the presence of an environment that does not promote tumour growth [68]. Surgical tumour excision helps cancer survive by altering the biological characteristics of neoplastic cells, such as proliferation, apoptosis, metastasis, and dormancy condition [70], and blood levels of tumour growth promoters (e.g., IL-6, TNF-α, VEGF) are higher after surgery, whereas antiangiogenic mediators such as endostatin and angiostatin are undetectable [71]. This finding supports the hypothesis that surgery and neuroendocrine mediators that control angiogenesis and inflammation can "awaken" a dormant tumour condition and dormant micrometastases [72]. As well, tumour angiogenic activity, which is the physiological process of generating new blood vessels from existing ones, is essential for the survival and development of tumour cells, including their growth, invasion and spread [73].

Even though some biological factors may paradoxically enhance the proliferation and dissemination of metastatic cells, surgical tumour removal provides an evident benefit in preventing the growth and spread of cancer [9]. Furthermore, both animal and human studies have demonstrated that the use of a less traumatic surgical technique and pharmaceutical substances, such as COX-2 selective nonsteroidal anti-inflammatory drugs [74,75], antithrombotics [63] and antiangiogenics [76,77], can make these biological effects simpler to control.

5. The Impact of the General Anaesthetics on the Immune System and Their "Anti-" and "Pro-Tumoral" Effects

Oncological diseases often require the use of anaesthetic and analgesic agents during diagnostic [78,79], therapeutic or palliative procedures to control pain [80,81] and minimise the effects of the stress response [76]. General anaesthetics include volatile agents like isoflurane and intravenous agents like propofol, which have been linked to immunomodulatory properties such as the inhibition of NK cell activity [82] and pro-tumour effects such as the inhibition of prostaglandin synthesis by tumour cells [47]. Due to their immunosuppressive effects, volatile anaesthesia may be associated with poorer outcomes than intravenous anaesthesia [83,84], as demonstrated in Figure 2. However, human studies suggest that general anaesthetics in combination with regional anaesthesia can reduce the inflammatory response and endothelial permeability, preventing the spread of cancer cells [65]. Also, studies in dogs and cats suggest that loco-regional therapy serves to reduce the quantity of intra and post-operative opioids, allowing their adverse effects to be reduced [85–87].

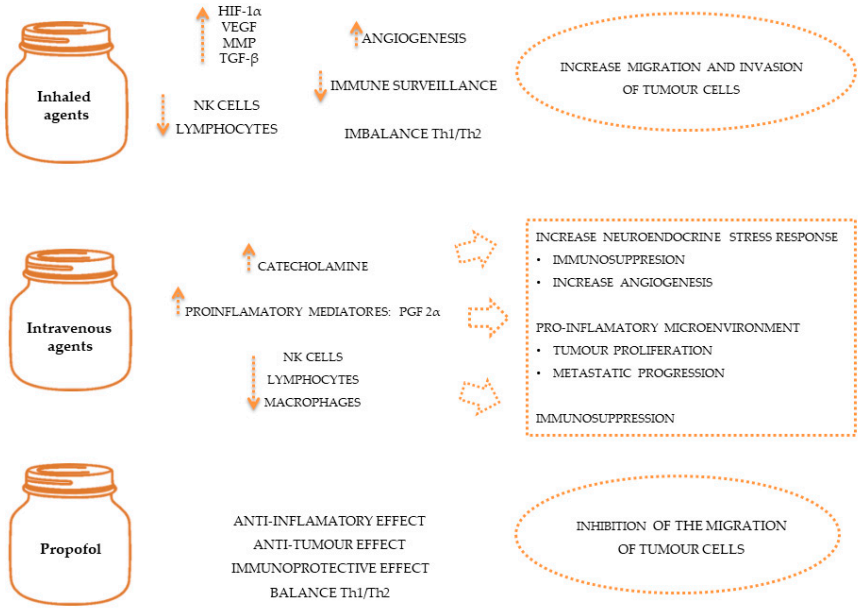


Figure 2. The effect of anaesthetics on immune system and on tumour spread.

5.1. Volatile Anaesthetic Agents

Volatile anaesthetics, such as isuflurane and sevoflurane, are halogenated agents used to induce and maintain general anaesthesia through the respiratory system [66] as well as regulate anaesthetic depth in real time, being useful in both short and long anaesthesia [88]. Depending on whether they are used solo or in combination, they can exhibit more or fewer effects on tumour cells and on the immune system [82]. In human research, volatile anaesthetic agents promote dose- and time-dependent immune suppression [89], inhibit lymphocyte proliferation [90] and reduce the function of natural killer (NK) cells, which play a crucial role in protecting against the spread of cancer cells [91]. Moreover, they affect the biological functions of macrophages, neutrophils and natural killer (NK) cells by enhancing anti-apoptosis pathway signalling [92] and modulating intracellular signals of cancer cell activity, such as proliferation, migration, invasion and chemoresistance [93,94]. Animal studies suggest that volatile anaesthetics suppress the immune system more than propofol [24], inhibit the cytotoxic activity of natural killer cells [82], reduce the secretion of TNF and IL-1 [95] and, when combined with propofol, maintain similar ratios of CD3+/anti-B cells and CD4+/CD8+ cells before and after anaesthesia [24].

Isuflurane is an inhaled anaesthetic agent commonly used in veterinary medicine that produces a state of unconsciousness due to its action on the central nervous system and without analgesic properties [96]. Like other inhalation anaesthetics of this type, it suppresses the respiratory and cardiovascular systems, is absorbed by inhalation and is rapidly distributed by tissues, including the brain [96]. Its absorption, distribution and elimination by the lungs are quick, with the clinical consequences of rapid induction and recovery and easy and rapid control of the depth of anaesthesia [96]. Several human studies have investigated the immunomodulatory effects of isuflurane, with results that may be less beneficial for cancer patients due to the fact that it suppresses the immune system significantly. Therefore, they suggest that isuflurane may lower the number of circulating NK cells [97], inhibit their activity [98] and reduce their ability to respond to INF-g stimulation [99]. They can also diminish the number of B lymphocytes, IFN-y, IFN-α, TNF-α and IL-2 circulated [97] as well as induce the apoptosis of B and T lymphocytes [98]. When compared to intravenous anaesthesia, isuflurane can more significantly diminish the ratio of Th1/Th2 lymphocytes [98], with no significant changes in CD4+ cells (helper T cells) [100]. General anaesthesia only with isuflurane can increase the levels of HIF-1α. However, this does not happen when it is associated with propofol, which is correlated with a reduction in cancer cells' malignant activity [92]. Their anti-inflammatory properties are induced by suppressing the NF-kB pathway [101], which regulates essential cellular processes including inflammatory responses, cellular growth and apoptosis, which are associated with certain conditions such as cancer [102]. Studies in vitro demonstrate that isuflurane can promote chemotherapeutic resistance in colon cancer cells [103] and enhance renal cancer growth and malignant potential [104]. Isuflurane also promotes the growth and migration of glioblastoma cells [105], increases the malignant potential of ovarian cancer cells through the up-regulation of markers associated with the cell cycle, proliferation, and angiogenesis [106] and enhances the proliferation of cervical cancer cells through the upregulation of histone [94]. Immune suppression and its effects on oncological patients were also observed in studies on animals anaesthetised with isuflurane, suggesting that this inhalant agent suppress the immune system more than propofol [24], inhibits the cytotoxic activity of natural killer cells [82] and decreases the secretion of TNF-α and IL-1 [95]. This effect may be associated with tumour metastasis or recurrence in the post-operative period [82]. In horses, isuflurane reduces the activity of the neutrophil myeloperoxidase desgranulation system [107], which contributes to the elimination of injured host tissues and invading microorganisms [108]. In dogs, it was shown that the combination of isuflurane with propofol can affect lymphocyte counts, which decreased considerably 24 h after anaesthesia, and the ratios of CD3+/anti-B cells and CD4+/CD8+ cells did not significantly differ before and after anaesthesia [24]. In mice, a significant increase in melanoma growth was observed when they were exposed to isuflurane [109].

Sevoflurane is an inhaled anaesthetic agent used to induce and maintain anaesthesia [96]. It produces a relatively quick and smooth start to anaesthesia in dogs, followed by an effective recovery [96]. Vomiting, decreased blood pressure, increased breathing rate, muscle tension, excitement, small muscle contractions and a temporary inability to breathe are the most common adverse effects of sevoflurane [96]. Human research has demonstrated that sevoflurane has the potential to inhibit NK cell activity, increase apoptosis in T and B lymphocyte cells [102] and suppress the release of IL-1β and TNF-α [90]. Both induce the dose-dependent inhibition of polymorphonuclear neutrophil apoptosis [110,111]. However, sevoflurane has no effect on the total lymphocyte count, decreasing the neutrophil and increasing the lymphocyte numbers [112]. Moreover, they promote the increased expression of HIF-1α [113] and inhibit the recruitment of macrophages [114]. Sevoflurane converts helper T cells into tumour-promoting T lymphocytes, decreasing the Th1/Th2 ratio [115]. Anaesthesia with sevoflurane may increase the levels of pro-tumour cytokines and metalloproteinases [116], have a systemic anti-inflammatory effect [117] and decrease hypoxia-induced growth and metastasis via suppressing HIF-1α [118]. They increase the survival of breast cancer cells via the modulation of intracellular Ca2+ homeostasis [93] and inhibit the viability, migration and invasion of osteosarcoma cells by inactivating the PI3K/ATK pathway [119], as well as the formation of lung cancer cells and metastasis by decreasing HIF-1α [95,120]. When combined with a spinal block, sevoflurane can limit the antitumor activity of liver mononuclear cells, probably by preserving the balance of Th1/Th2, preventing tumour spread [121]. In animal models, sevoflurane converts helper T cells into tumour-promoting T lymphocytes, decreasing the Th1/Th2 ratio which has been linked to the development and spread of canine cancer [37]. Moreover, sevoflurane plays an important role in regulating gene expression by inducing different mRNA expression [122], which is the primary molecular mechanism responsible for the pathological processes of human diseases, including cancer [123]. According to a rabbit study, the suppression of leukocyte subpopulations (CD45+, CD4+, CD8+, and CD21+ cells) increased by anaesthesia with sevoflurane alone or in combination with nitrous oxide [124]. On canine mammary tumour cells, sevoflurane at low concentrations demonstrated a significant increase in cell proliferation, whereas it was inhibited at high concentrations [125].

5.2. Intravenous Anaesthetic Agents

Propofol, alphaxalone and ketamine are all commonly used for the induction, co-induction and maintenance of anaesthesia [126–128]. They may be administered alone or in combination with other intravenous agents, volatile anaesthetics [92] or other techniques such as regional anaesthesia [129]. According to human and animal studies, certain intravenous agents induce protective immune effects, inhibiting tumour growth [24,130]. However, in vitro research with dog models did not reveal any effect of propofol, alphaxalone or ketamine on the cytotoxic activity of peripheral lymphocytes, albeit researchers acknowledge that these anaesthetics' actions in a living organism could have different results [131]. Nonetheless, other studies have shown different findings, demonstrating that some of intravenous anaesthetic agents may promote the proliferation and migration of human breast cancer cell lines and oral squamous cell carcinoma [132,133].

Propofol (2,6-diisopropylphenol) is one of the intravenous anaesthetic agents routinely used in veterinary clinical practice for the induction and maintenance of general anaesthesia, with affinity for γ-aminobutyric acid (GABA) receptors and producing sedative and hypnotic effects [134]. They possess neuroprotective [135], anti-apoptotic [136] and anti-inflammatory actions in the central nervous system [137]. Metabolites of propofol inhibit the oxidant activities of neutrophils and myeloperoxidase and can have immunomodulatory effects during clinical use, particularly for the treatment of systemic diseases such as cancer [138]. Moreover, in human medicine, propofol is gaining emphasis in oncological surgery due to its "immunoprotective" [24] and "anti-tumoral" [130] properties, which are able to alter the biological characteristics of tumours by promoting the apoptosis of tumour cells, increasing tumour sensitivity to various chemotherapeutic agents [139] and decreas-

ing the activity of tumour cells [92]. They also decrease the production of inflammatory mediators [140,141] and the immunity of the tumour microenvironment [142], modulating intrinsic processes such as neoangiogenesis [143]. In dogs anaesthetised with propofol, lower blood concentrations of catecholamines and cortisol have been demonstrated, suggesting less anaesthetic stress when compared to isuflurane [144]. Propofol inhibits the synthesis of prostaglandins by canine tumour cells and has no effect on the activity of lymphocytes and natural killer cells [47], as well as on the pro- and anti-inflammatory cytokines [24], reducing variations in the distribution of lymphocytes [145] and having no effect on the ratio of B/T cells and CD3+/CD8+ lymphocytes [82]. Moreover, they do not alter the balance of the Th1/Th2 lymphocyte ratio [100], which is associated with a slower progression and spread of tumour cells [37] and prevents the activation of HIF-1α by tissue hypoxia [92]. Dogs with diffuse large B-cell lymphoma anaesthetised with a volatile agent such as isuflurane or sevoflurane, opioids or propofol have a high risk of lymphoma relapse; however, the authors suggest that the results may have been caused by the opioids and inhalant agents [146]. In mice with breast cancer metastases, researchers compared the effects of propofol to those of ketamine, thiopental and halothane, suggesting that propofol has a small influence on NK cell function without promoting the growth of metastases [91]. In murine, a study suggests that propofol can directly suppress COX enzyme activity in peritoneal macrophages [147] and in human monocytes [148] which have been shown to promote tumour progression [49]. Studies in vitro with a rat model revealed that propofol inhibits tumour development by maintaining cytotoxic lymphocyte function [149]. A human study indicated that the risk of recurrence of oncological disease is substantially reduced when both propofol and epidural anaesthesia are used [150]. In addition, in humans, propofol-based anaesthesia during mastectomy is associated with increased survival compared to inhaled anaesthesia [150] and has an antitumor effect on rectal cancer by reducing the invasion capacity of this type of tumour cell [151]. In human lung cancer surgery, propofol maintains Th17/Treg cell balance through the GABA A receptor [152], which is important in regulating autoimmunity and cancer [153]. On the other hand, in vitro studies demonstrated that propofol promotes the migration and invasion of oral squamous cell carcinoma cells by upregulating the expression of the snail family transcriptional repressor 1 [132], which promotes tumour development in a variety of cancers and whose expression is related to the tumour grade and lymph node metastasis [154]. Using the Th1/Th2 ratio as an indicator, studies with patients undergoing craniotomy suggest that propofol can suppress the immune response induced by surgical stress [100].

Total intravenous anaesthesia (TIVA) is defined as the induction and maintenance of anaesthesia achieved exclusively by intravenous (IV) drugs [155]. This approach provides high hemodynamic stability, a smooth recovery and minimises exposure to inhalant anaesthetics [155]. Using propofol-based TIVA, a balanced anaesthesia approach is suggested in order to limit this agent's dosage [156]. Propofol has advantageous pharmacokinetic properties for use in TIVA, including a quick onset, a brief duration of action and non-accumulative effects [157]. By combining different agents (anaesthetics, analgesics and/or sedatives) and anaesthetic techniques (loco-regional or neuraxial), it allows the reduction in each drug's dose and its dose-dependent adverse effects while also delivering analgesia [129]. Immunoprotective effects, especially in T-lymphocytes and in pro- and anti-inflammatory cytokines, have been observed in dogs under general anaesthesia only using propofol [24,158]. In human studies, comparing TIVA with a volatile anaesthetic demonstrated that the number of CD3+, CD4+ and CD8+ T-lymphocytes decreased less following TIVA [159] and those who receive propofol-based TIVA during cancer surgery have higher overall survival [160].

Alfaxalone (3a-hydroxy-5a-pregnane-11, 20-dione) is a neurosteroid anaesthetic that interacts with the gamma aminobutyric acid A receptor, producing anaesthesia and muscle relaxation [161]. Moreover, studies in dogs and cats suggest no beneficial analgesic effect of alfaxalone compared with propofol [162–164]. Studies in vitro have shown the impact of alfaxalone on canine peripheral blood lymphocyte function and did not find any influence.

However, the authors of this manuscript acknowledge that the effects of various anaesthetics on a living organism could vary [131]. Studies in rats demonstrate that alphaxalone could effectively inhibit the proliferation of C6 glioma cells [165] as well as the histamine release from mast cells [166]. Due to an absence of research, the effect of alfaxalone on the immune system and on tumour cells is still unknown.

Ketamine is a phenylcyclohexylamine derivative and antagonist of the excitatory neurotransmitter N-methyl-D-aspartate (NMDA) receptors [167]. It is well known for its dissociative anaesthetic qualities, but it also has antihyperalgesic [168] and anti-inflammatory effects, described in both in human [169] and laboratory animals [170,171]. The anti-proinflammatory effect of ketamine is indeed associated with its capacity to regulate cytokines and inflammatory mediators, as well as recruit inflammatory cells. [169]. Ketamine can lessen the demand for opioids [172] and their immunosuppressive effects [173], as well as enhance morphine's effectiveness in cancer pain management [174]. Animal studies suggest that ketamine can inhibit NK cell activity and circulating numbers, resulting in increased metastasis [91]. These findings also suggest that, in vivo, this drug can suppress the immune system via stimulation of the sympathetic nervous system, explaining why β-receptor antagonists can diminish the pro-metastatic effects of ketamine [91]. On the other hand, in vitro studies demonstrated that the effect of ketamine on the cytotoxicity of peripheral lymphocytes was insignificant [131]. On an equine macrophage cell line, ketamine inhibited lipopolysaccharide-induced TNF-α and IL-6 [175]. In a rat model, ketamine promoted lung metastasis via NK cell suppression [91] and decreased the DC production of IL-12, indicating that this drug profoundly influenced T cell differentiation [176] as well as stimulated the development of metastases in lung carcinomas [151]. Human studies report that low preoperative doses of ketamine maintained IL-2 expression, which is crucial for preventing autoimmunity and T-cell differentiation, but once pain is a suppressor of IL-2 release, it is unclear as to whether this result was a direct effect or a consequence of the analgesic effect [177]. Moreover, ketamine causes the apoptosis of T lymphocytes [178] and inhibits the functional maturation of dendritic cells [176]. They also block the NMDA receptor to promote anti-tumour actions [179] as well as inhibit the differentiation of monocytes into immature DCs and the beta TGF-dependent process [180].

6. Conclusions

The influence of surgery and anaesthetic agents on the immune system and tumour cells is still uncertain. Despite several studies, the controversial outcomes remain a fact and can be attributed to distinct experimental conditions, such as in vitro or in vivo research, the type of cell line, surgical technique, and anaesthetic agents and their concentration. Moreover, we know that the perioperative period is a time when the body is more susceptible to developing a compromised immune response and, consequently, an increased risk of tumour dissemination. However, this time can be seen as an opportunity to control or minimise the impact of anaesthetic and surgical effects. After reviewing the above studies, propofol-based anaesthesia appears to have immunoprotective and anti-tumour effects and has been shown to decrease surgical stress, immunosuppression and angiogenesis. On the other hand, inhaled anaesthetics have been associated with a higher rate of tumour recurrence and metastasis because of their capacity to induce pro-inflammatory activity and decrease immune function. As well, minimally invasive surgery, when compared with open surgery, shows major tissue protection and minor stress responses. However, it has been linked to prolonged surgical and anaesthetic times.

Through the new anaesthesia and surgery strategy, the perioperative period is already recognised as a window of opportunity for minimising their side effects. To draw definitive conclusions about the outcomes of surgery and anaesthesia in oncology patients, additional clinical trials are required.

Funding: This work was supported by the projects UIDB/CVT/00772/2020 and LA/P/0059/2020 funded by the Portuguese Foundation for Science and Technology (FCT).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting the findings of this study are shown in the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Wemelsfelder, F.; Mullan, S. Applying Ethological and Health Indicators to Practical Animal Welfare Assessment. *Rev. Sci. Tech. OIE* **2014**, *33*, 111–120. [CrossRef] [PubMed]
2. Alexander, J.E.; Colyer, A.; Haydock, R.M.; Hayek, M.G.; Park, J. Understanding How Dogs Age: Longitudinal Analysis of Markers of Inflammation, Immune Function, and Oxidative Stress. *J. Gerontol. Ser. A* **2018**, *73*, 720–728. [CrossRef]
3. Pinello, K.; Amorim, I.; Pires, I.; Canadas-Sousa, A.; Catarino, J.; Faísca, P.; Branco, S.; Peleteiro, M.C.; Silva, D.; Severo, M.; et al. Vet-OncoNet: Malignancy Analysis of Neoplasms in Dogs and Cats. *Vet. Sci.* **2022**, *9*, 535. [CrossRef] [PubMed]
4. Rafalko, J.M.; Kruglyak, K.M.; McCleary-Wheeler, A.L.; Goyal, V.; Phelps-Dunn, A.; Wong, L.K.; Warren, C.D.; Brandstetter, G.; Rosentel, M.C.; DiMarzio, L.; et al. Age at Cancer Diagnosis by Breed, Weight, Sex, and Cancer Type in a Cohort of More than 3,000 Dogs: Determining the Optimal Age to Initiate Cancer Screening in Canine Patients. *PLoS ONE* **2023**, *18*, e0280795. [CrossRef] [PubMed]
5. Hong, H.; Wang, Q.; Li, J.; Liu, H.; Meng, X.; Zhang, H. Aging, Cancer and Immunity. *J. Cancer* **2019**, *10*, 3021–3027. [CrossRef]
6. Schwartz, S.M.; Urfer, S.R.; White, M.; Megquier, K.; Shrager, S.; The Dog Aging Project Consortium; Ruple, A. Lifetime Prevalence of Malignant and Benign Tumours in Companion Dogs: Cross-sectional Analysis of Dog Aging Project Baseline Survey. *Vet. Comp. Oncol.* **2022**, *20*, 797–804. [CrossRef]
7. Fleming, J.M.; Creevy, K.E.; Promislow, D.E.L. Mortality in North American Dogs from 1984 to 2004: An Investigation into Age-, Size-, and Breed-Related Causes of Death: Mortality of Dogs in North America. *J. Vet. Intern. Med.* **2011**, *25*, 187–198. [CrossRef]
8. Smith, A.N. Advances in Veterinary Oncology. *Vet. Clin. N. Am. Small Anim. Pract.* **2014**, *44*, xi–xii. [CrossRef]
9. Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *Eur. J. Cancer* **2009**, *45*, 228–247. [CrossRef]
10. Shibata, J.; Ishihara, S.; Tada, N.; Kawai, K.; Tsuno, N.H.; Yamaguchi, H.; Sunami, E.; Kitayama, J.; Watanabe, T. Surgical Stress Response after Colorectal Resection: A Comparison of Robotic, Laparoscopic, and Open Surgery. *Tech. Coloproctol.* **2015**, *19*, 275–280. [CrossRef]
11. Hume, K.R.; Johnson, J.L.; Williams, L.E. Adverse Effects of Concurrent Carboplatin Chemotherapy and Radiation Therapy in Dogs. *J. Vet. Intern. Med.* **2009**, *23*, 24–30. [CrossRef] [PubMed]
12. Wendelburg, K.M.; Price, L.L.; Burgess, K.E.; Lyons, J.A.; Lew, F.H.; Berg, J. Survival Time of Dogs with Splenic Hemangiosarcoma Treated by Splenectomy with or without Adjuvant Chemotherapy: 208 Cases (2001–2012). *J. Am. Vet. Med. Assoc.* **2015**, *247*, 393–403. [CrossRef] [PubMed]
13. McNally, A.; Rossanese, M.; Suárez-Bonnet, A.; Hardas, A.; Yale, A.D. Urinary Bladder Hemangiosarcoma in a Cat Treated with Partial Cystectomy and Adjuvant Metronomic Cyclophosphamide and Thalidomide. *Vet. Intern. Med.* **2023**, *37*, 1488–1492. [CrossRef] [PubMed]
14. Riggs, J.; Adams, V.J.; Hermer, J.V.; Dobson, J.M.; Murphy, S.; Ladlow, J.F. Outcomes Following Surgical Excision or Surgical Excision Combined with Adjunctive, Hypofractionated Radiotherapy in Dogs with Oral Squamous Cell Carcinoma or Fibrosarcoma. *J. Am. Vet. Med. Assoc.* **2018**, *253*, 73–83. [CrossRef]
15. Inbar, S.; Neeman, E.; Avraham, R.; Benish, M.; Rosenne, E.; Ben-Eliyahu, S. Do Stress Responses Promote Leukemia Progression? An Animal Study Suggesting a Role for Epinephrine and Prostaglandin-E2 through Reduced NK Activity. *PLoS ONE* **2011**, *6*, e19246. [CrossRef]
16. Goldfarb, Y.; Sorski, L.; Benish, M.; Levi, B.; Melamed, R.; Ben-Eliyahu, S. Improving Postoperative Immune Status and Resistance to Cancer Metastasis: A Combined Perioperative Approach of Immunostimulation and Prevention of Excessive Surgical Stress Responses. *Ann. Surg.* **2011**, *253*, 798–810. [CrossRef]
17. Lee, Y.N. Effect of Anesthesia and Surgery on Immunity. *J. Surg. Oncol.* **1977**, *9*, 425–430. [CrossRef]
18. Ogawa, K.; Hirai, M.; Katsube, T.; Murayama, M.; Hamaguchi, K.; Shimakawa, T.; Naritake, Y.; Hosokawa, T.; Kajiwara, T. Suppression of Cellular Immunity by Surgical Stress. *Surgery* **2000**, *127*, 329–336. [CrossRef]
19. Lin, L.; Liu, C.; Tan, H.; Ouyang, H.; Zhang, Y.; Zeng, W. Anaesthetic Technique May Affect Prognosis for Ovarian Serous Adenocarcinoma: A Retrospective Analysis. *Br. J. Anaesth.* **2011**, *106*, 814–822. [CrossRef]
20. Desborough, J.P. The Stress Response to Trauma and Surgery. *Br. J. Anaesth.* **2000**, *85*, 109–117. [CrossRef]
21. Novitsky, Y.W.; Litwin, D.E.M.; Callery, M.P. The Net Immunologic Advantage of Laparoscopic Surgery. *Surg. Endosc.* **2004**, *18*, 1411–1419. [CrossRef]
22. Dourado, A.; Gomes, A.; Teixeira, P.; Lobo, L.; Azevedo, J.T.; Dias, I.R.; Pinelas, R. Antinociceptive Effect of a Sacro-Coccygeal Epidural of Morphine and Lidocaine in Cats Undergoing Ovariohysterectomy. *Vet. Sci.* **2022**, *9*, 623. [CrossRef] [PubMed]
23. White, D.M.; Mair, A.R.; Martinez-Taboada, F. Opioid-Free Anaesthesia in Three Dogs. *Open Vet. J.* **2017**, *7*, 104. [CrossRef]

24. Tomihari, M.; Nishihara, A.; Shimada, T.; Yanagawa, M.; Miyoshi, M.; Miyahara, K.; Oishi, A. A Comparison of the Immunological Effects of Propofol and Isoflurane for Maintenance of Anesthesia in Healthy Dogs. *J. Vet. Med. Sci.* **2015**, *77*, 1227–1233. [CrossRef] [PubMed]
25. Yeo, J.; Park, J.S.; Choi, G.-S.; Kim, H.J.; Kim, J.K.; Oh, J.; Park, S.Y. Comparison of the Analgesic Efficacy of Opioid-Sparing Multimodal Analgesia and Morphine-Based Patient-Controlled Analgesia in Minimally Invasive Surgery for Colorectal Cancer. *World J. Surg.* **2022**, *46*, 1788–1795. [CrossRef]
26. Carvalho, M.I.; Pires, I.; Prada, J.; Ferreira, A.F.; Queiroga, F.L. Positive Interplay Between CD3+ T-Lymphocytes and Concurrent COX-2/EGFR Expression in Canine Malignant Mammary Tumors. *Anticancer Res.* **2015**, *35*, 2915–2920.
27. Vivier, E.; Tomasello, E.; Baratin, M.; Walzer, T.; Ugolini, S. Functions of Natural Killer Cells. *Nat. Immunol.* **2008**, *9*, 503–510. [CrossRef] [PubMed]
28. Raskov, H.; Orhan, A.; Christensen, J.P.; Gögenur, I. Cytotoxic CD8+ T Cells in Cancer and Cancer Immunotherapy. *Br. J. Cancer* **2021**, *124*, 359–367. [CrossRef]
29. Lee, Y.S.; Radford, K.J. The Role of Dendritic Cells in Cancer. In *International Review of Cell and Molecular Biology*; Elsevier: Amsterdam, The Netherlands, 2019; Volume 348, pp. 123–178, ISBN 978-0-12-818351-9.
30. Mittal, D.; Gubin, M.M.; Schreiber, R.D.; Smyth, M.J. New Insights into Cancer Immunoediting and Its Three Component Phases—Elimination, Equilibrium and Escape. *Curr. Opin. Immunol.* **2014**, *27*, 16–25. [CrossRef]
31. Petrucci, G.N.; Lobo, L.; Queiroga, F.; Martins, J.; Prada, J.; Pires, I.; Henriques, J. Neutrophil-to-lymphocyte Ratio Is an Independent Prognostic Marker for Feline Mammary Carcinomas. *Vet. Comp. Oncol.* **2021**, *19*, 482–491. [CrossRef]
32. Marconato, L.; Martini, V.; Stefanello, D.; Moretti, P.; Ferrari, R.; Comazzi, S.; Laganga, P.; Riondato, F.; Aresu, L. Peripheral Blood Lymphocyte/Monocyte Ratio as a Useful Prognostic Factor in Dogs with Diffuse Large B-Cell Lymphoma Receiving Chemoimmunotherapy. *Vet. J.* **2015**, *206*, 226–230. [CrossRef] [PubMed]
33. Zhang, L.; Conejo-Garcia, J.R.; Katsaros, D.; Gimotty, P.A.; Massobrio, M.; Regnani, G.; Makrigiannakis, A.; Gray, H.; Schlienger, K.; Liebman, M.N.; et al. Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer. *N. Engl. J. Med.* **2003**, *348*, 203–213. [CrossRef] [PubMed]
34. Sato, E.; Olson, S.H.; Ahn, J.; Bundy, B.; Nishikawa, H.; Qian, F.; Jungbluth, A.A.; Frosina, D.; Gnjatic, S.; Ambrosone, C.; et al. Intraepithelial CD8 $^{+}$ Tumor-Infiltrating Lymphocytes and a High CD8^{+}/Regulatory T Cell Ratio Are Associated with Favorable Prognosis in Ovarian Cancer. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 18538–18543. [CrossRef]
35. Macfarlane, M.J.; Macfarlane, L.L.; Scase, T.; Parkin, T.; Morris, J.S. Use of Neutrophil to Lymphocyte Ratio for Predicting Histopathological Grade of Canine Mast Cell Tumours. *Vet. Rec.* **2016**, *179*, 491. [CrossRef]
36. Sottnik, J.L.; Rao, S.; Lafferty, M.H.; Thamm, D.H.; Morley, P.S.; Withrow, S.J.; Dow, S.W. Association of Blood Monocyte and Lymphocyte Count and Disease-Free Interval in Dogs with Osteosarcoma: CBC Is Prognostic in Osteosarcoma. *J. Vet. Intern. Med.* **2010**, *24*, 1439–1444. [CrossRef]
37. Horiuchi, Y.; Hanazawa, A.; Nakajima, Y.; Nariai, Y.; Asanuma, H.; Kuwabara, M.; Yukawa, M.; Ito, H. T-Helper (Th) 1/Th2 Imbalance in the Peripheral Blood of Dogs with Malignant Tumor. *Microbiol. Immunol.* **2007**, *51*, 1135–1138. [CrossRef] [PubMed]
38. Kim, J.-H.; Chon, S.-K.; Im, K.-S.; Kim, N.-H.; Sur, J.-H. Correlation of Tumor-Infiltrating Lymphocytes to Histopathological Features and Molecular Phenotypes in Canine Mammary Carcinoma: A Morphologic and Immunohistochemical Morphometric Study. *Can. J. Vet. Res.* **2013**, *77*, 142–149.
39. Carvalho, M.I.; Pires, I.; Prada, J.; Queiroga, F.L. A Role for T-Lymphocytes in Human Breast Cancer and in Canine Mammary Tumors. *BioMed Res. Int.* **2014**, *2014*, 130894. [CrossRef]
40. Goswami, S.; Sahai, E.; Wyckoff, J.B.; Cammer, M.; Cox, D.; Pixley, F.J.; Stanley, E.R.; Segall, J.E.; Condeelis, J.S. Macrophages Promote the Invasion of Breast Carcinoma Cells via a Colony-Stimulating Factor-1/Epidermal Growth Factor Paracrine Loop. *Cancer Res.* **2005**, *65*, 5278–5283. [CrossRef]
41. Biswas, S.K.; Mantovani, A. Macrophage Plasticity and Interaction with Lymphocyte Subsets: Cancer as a Paradigm. *Nat. Immunol.* **2010**, *11*, 889–896. [CrossRef]
42. De Monte, L.; Reni, M.; Tassi, E.; Clavenna, D.; Papa, I.; Recalde, H.; Braga, M.; Di Carlo, V.; Doglioni, C.; Protti, M.P. Intratumor T Helper Type 2 Cell Infiltrate Correlates with Cancer-Associated Fibroblast Thymic Stromal Lymphopoietin Production and Reduced Survival in Pancreatic Cancer. *J. Exp. Med.* **2011**, *208*, 469–478. [CrossRef] [PubMed]
43. Tosolini, M.; Kirilovsky, A.; Mlecnik, B.; Fredriksen, T.; Mauger, S.; Bindea, G.; Berger, A.; Bruneval, P.; Fridman, W.-H.; Pagès, F.; et al. Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer. *Cancer Res.* **2011**, *71*, 1263–1271. [CrossRef] [PubMed]
44. Gültekin, Ç. Comparison of the Analgesic Effects of Morphine and Tramadol after Tumor Surgery in Dogs. *Open Vet. J.* **2021**, *11*, 613. [CrossRef]
45. Thaker, P.H.; Han, L.Y.; Kamat, A.A.; Arevalo, J.M.; Takahashi, R.; Lu, C.; Jennings, N.B.; Armaiz-Pena, G.; Bankson, J.A.; Ravoori, M.; et al. Chronic Stress Promotes Tumor Growth and Angiogenesis in a Mouse Model of Ovarian Carcinoma. *Nat. Med.* **2006**, *12*, 939–944. [CrossRef] [PubMed]
46. Miyata, T.; Honma, R.; Sato, A.; Matsumoto, H.; Koyama, H.; Tagawa, M. Effect of rCaIFN-γ Pretreatment on Propofol–Isoflurane Suppression of NK Cytotoxic Activity in the Peripheral Blood of Dogs. *Res. Vet. Sci.* **2015**, *98*, 25–29. [CrossRef] [PubMed]

47. Matsumoto, H.; Miyata, T.; Ohkusa, T.; Teshima, T.; Koyama, H. Effects of Recombinant Canine Interferon-γ Injected before General Anesthesia with Propofol and Isoflurane on Natural Killer Cytotoxic Activity during Anesthesia in Dogs. *Res. Vet. Sci.* **2019**, *125*, 416–420. [CrossRef]
48. Hashemi Goradel, N.; Najafi, M.; Salehi, E.; Farhood, B.; Mortezaee, K. Cyclooxygenase-2 in Cancer: A Review. *J. Cell. Physiol.* **2019**, *234*, 5683–5699. [CrossRef]
49. Hashemi, V.; Maleki, L.A.; Esmaily, M.; Masjedi, A.; Ghalamfarsa, G.; Namdar, A.; Yousefi, M.; Yousefi, B.; Jadidi-Niaragh, F. Regulatory T Cells in Breast Cancer as a Potent Anti-Cancer Therapeutic Target. *Int. Immunopharmacol.* **2020**, *78*, 106087. [CrossRef]
50. Terhune, J.; Berk, E.; Czerniecki, B. Dendritic Cell-Induced Th1 and Th17 Cell Differentiation for Cancer Therapy. *Vaccines* **2013**, *1*, 527–549. [CrossRef]
51. Ma, Y.; Shurin, G.V.; Peiyuan, Z.; Shurin, M.R. Dendritic Cells in the Cancer Microenvironment. *J. Cancer* **2013**, *4*, 36–44. [CrossRef]
52. Tvedskov, T.F.; Jensen, M.-B.; Kroman, N.; Balslev, E. Iatrogenic Displacement of Tumor Cells to the Sentinel Node after Surgical Excision in Primary Breast Cancer. *Breast Cancer Res. Treat.* **2012**, *131*, 223–229. [CrossRef] [PubMed]
53. Raven, R.W. Surgical Oncology-Theory and Practice. *J. Surg. Oncol.* **2006**, *30*, 145–148. [CrossRef]
54. Curtin, J.; Thomson, P.; Wong, G.; Lam, A.; Choi, S.-W. The Impact of Surgery on Circulating Malignant Tumour Cells in Oral Squamous Cell Carcinoma. *Cancers* **2023**, *15*, 584. [CrossRef] [PubMed]
55. Bogden, A.; Moreau, J.-P.; Eden, P. Proliferative Response of Human and Animal Tumours to Surgical Wounding of Normal Tissues: Onset, Duration and Inhibition. *Br. J. Cancer* **1997**, *75*, 1021–1027. [CrossRef]
56. Demicheli, R.; Miceli, R.; Moliterni, A.; Zambetti, M.; Hrushesky, W.J.M.; Retsky, M.W.; Valagussa, P.; Bonadonna, G. Breast Cancer Recurrence Dynamics Following Adjuvant CMF Is Consistent with Tumor Dormancy and Mastectomy-Driven Acceleration of the Metastatic Process. *Ann. Oncol.* **2005**, *16*, 1449–1457. [CrossRef] [PubMed]
57. Li, T.-S.; Kaneda, Y.; Ueda, K.; Hamano, K.; Zempo, N.; Esato, K. The Influence of Tumour Resection on Angiostatin Levels and Tumour Growth—An Experimental Study in Tumour-Bearing Mice. *Eur. J. Cancer* **2001**, *37*, 2283–2288. [CrossRef]
58. Shiozawa, Y.; Pedersen, E.A.; Havens, A.M.; Jung, Y.; Mishra, A.; Joseph, J.; Kim, J.K.; Patel, L.R.; Ying, C.; Ziegler, A.M.; et al. Human Prostate Cancer Metastases Target the Hematopoietic Stem Cell Niche to Establish Footholds in Mouse Bone Marrow. *J. Clin. Investig.* **2011**, *121*, 1298–1312. [CrossRef]
59. Patel, H.; Le Marer, N.; Wharton, R.Q.; Khan, Z.A.J.; Araia, R.; Glover, C.; Henry, M.M.; Allen-Mersh, T.G. Clearance of Circulating Tumor Cells after Excision of Primary Colorectal Cancer. *Ann. Surg.* **2002**, *235*, 226–231. [CrossRef]
60. Hüsemann, Y.; Geigl, J.B.; Schubert, F.; Musiani, P.; Meyer, M.; Burghart, E.; Forni, G.; Eils, R.; Fehm, T.; Riethmüller, G.; et al. Systemic Spread Is an Early Step in Breast Cancer. *Cancer Cell* **2008**, *13*, 58–68. [CrossRef]
61. Tremblay, P.-L.; Huot, J.; Auger, F.A. Mechanisms by Which E-Selectin Regulates Diapedesis of Colon Cancer Cells under Flow Conditions. *Cancer Res.* **2008**, *68*, 5167–5176. [CrossRef]
62. Rahbari, N.N.; Aigner, M.; Thorlund, K.; Mollberg, N.; Motschall, E.; Jensen, K.; Diener, M.K.; Büchler, M.W.; Koch, M.; Weitz, J. Meta-Analysis Shows That Detection of Circulating Tumor Cells Indicates Poor Prognosis in Patients with Colorectal Cancer. *Gastroenterology* **2010**, *138*, 1714–1726.e13. [CrossRef]
63. Seth, R.; Tai, L.H.; Falls, T.; De Souza, C.T.; Bell, J.C.; Carrier, M.; Atkins, H.; Boushey, R.; Auer, R.A. Surgical Stress Promotes the Development of Cancer Metastases by a Coagulation-Dependent Mechanism Involving Natural Killer Cells in a Murine Model. *Ann. Surg.* **2013**, *258*, 158–168. [CrossRef] [PubMed]
64. Bachman, S.L.; Hanly, E.J.; Nwanko, J.I.; Lamb, J.; Herring, A.E.; Marohn, M.R.; De Maio, A.; Talamini, M.A. The Effect of Timing of Pneumoperitoneum on the Inflammatory Response. *Surg. Endosc. Other Interv. Tech.* **2004**, *18*, 1640–1644. [CrossRef] [PubMed]
65. Cummings III, K.C.; Zimmerman, N.M.; Maheshwari, K.; Cooper, G.S.; Cummings, L.C. Epidural Compared with Non-Epidural Analgesia and Cardiopulmonary Complications after Colectomy: A Retrospective Cohort Study of 20,880 Patients Using a National Quality Database. *J. Clin. Anesth.* **2018**, *47*, 12–18. [CrossRef]
66. Sakai, E.M.; Connolly, L.A.; Klauck, J.A. Inhalation Anesthesiology and Volatile Liquid Anesthetics: Focus on Isoflurane, Desflurane, and Sevoflurane. *Pharmacotherapy* **2005**, *25*, 1773–1788. [CrossRef]
67. Park, Y.; Ha, J.W. Comparison of One-Level Posterior Lumbar Interbody Fusion Performed With a Minimally Invasive Approach or a Traditional Open Approach. *Spine* **2007**, *32*, 537–543. [CrossRef]
68. Zappalà, G.; McDonald, P.G.; Cole, S.W. Tumor Dormancy and the Neuroendocrine System: An Undisclosed Connection? *Cancer Metastasis Rev.* **2013**, *32*, 189–200. [CrossRef] [PubMed]
69. Aguirre-Ghiso, J.A. Models, Mechanisms and Clinical Evidence for Cancer Dormancy. *Nat. Rev. Cancer* **2007**, *7*, 834–846. [CrossRef]
70. Schmidt-Kittler, O.; Ragg, T.; Daskalakis, A.; Granzow, M.; Ahr, A.; Blankenstein, T.J.F.; Kaufmann, M.; Diebold, J.; Arnholdt, H.; Müller, P.; et al. From Latent Disseminated Cells to Overt Metastasis: Genetic Analysis of Systemic Breast Cancer Progression. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7737–7742. [CrossRef]
71. O'Reilly, M.S.; Holmgren, L.; Shing, Y.; Chen, C.; Rosenthal, R.A.; Moses, M.; Lane, W.S.; Cao, Y.; Sage, E.H.; Folkman, J. Angiostatin: A Novel Angiogenesis Inhibitor That Mediates the Suppression of Metastases by a Lewis Lung Carcinoma. *Cell* **1994**, *79*, 315–328. [CrossRef]
72. Varani, J.; Lovett, E.J.; Lundy, J. A Model of Tumor Cell Dormancy: Effects of Anesthesia and Surgery. *J. Surg. Oncol.* **1981**, *17*, 9–14. [CrossRef]

73. Yang, H.; Lee, S.; Lee, S.; Kim, K.; Yang, Y.; Kim, J.H.; Adams, R.H.; Wells, J.M.; Morrison, S.J.; Koh, G.Y.; et al. Sox17 Promotes Tumor Angiogenesis and Destabilizes Tumor Vessels in Mice. *J. Clin. Investig.* **2013**, *123*, 418–431. [CrossRef]
74. Queiroga, F.L.; Pires, I.; Parente, M.; Gregório, H.; Lopes, C.S. COX-2 over-Expression Correlates with VEGF and Tumour Angiogenesis in Canine Mammary Cancer. *Vet. J.* **2011**, *189*, 77–82. [CrossRef] [PubMed]
75. Sui, W.; Zhang, Y.; Wang, Z.; Wang, Z.; Jia, Q.; Wu, L.; Zhang, W. Antitumor Effect of a Selective COX-2 Inhibitor, Celecoxib, May Be Attributed to Angiogenesis Inhibition through Modulating the PTEN/PI3K/Akt/HIF-1 Pathway in an H22 Murine Hepatocarcinoma Model. *Oncol. Rep.* **2014**, *31*, 2252–2260. [CrossRef] [PubMed]
76. Li, Q.; Wang, Y.; Jia, W.; Deng, H.; Li, G.; Deng, W.; Chen, J.; Kim, B.Y.S.; Jiang, W.; Liu, Q.; et al. Low-Dose Anti-Angiogenic Therapy Sensitizes Breast Cancer to PD-1 Blockade. *Clin. Cancer Res.* **2020**, *26*, 1712–1724. [CrossRef] [PubMed]
77. Huang, Y.; Yuan, J.; Righi, E.; Kamoun, W.S.; Ancukiewicz, M.; Nezivar, J.; Santosuosso, M.; Martin, J.D.; Martin, M.R.; Vianello, F.; et al. Vascular Normalizing Doses of Antiangiogenic Treatment Reprogram the Immunosuppressive Tumor Microenvironment and Enhance Immunotherapy. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 17561–17566. [CrossRef] [PubMed]
78. De Bonis, A.; Collivignarelli, F.; Paolini, A.; Falerno, I.; Rinaldi, V.; Tamburro, R.; Bianchi, A.; Terragni, R.; Gianfelici, J.; Frescura, P.; et al. Sentinel Lymph Node Mapping with Indirect Lymphangiography for Canine Mast Cell Tumour. *Vet. Sci.* **2022**, *9*, 484. [CrossRef] [PubMed]
79. Karayannopoulou, M.; Anagnostou, T.; Margariti, A.; Kritsepi-Konstantinou, M.; Psalla, D.; Savvas, I.; Kazakos, G. Effect of Anaesthesia on Cell-Mediated Immunity in Dogs Undergoing Mastectomy for Mammary Cancer. *Vet. Anaesth. Analg.* **2022**, *49*, 265–274. [CrossRef]
80. Gaynor, J.S. Control of Cancer Pain in Veterinary Patients. *Vet. Clin. N. Am. Small Anim. Pract.* **2008**, *38*, 1429–1448. [CrossRef]
81. Te Boveldt, N.; Vernooij-Dassen, M.; Burger, N.; Vissers, K.; Engels, Y. Pain and Its Interference with Daily Activitiesin Medical Oncology Outpatients. *Pain Phys.* **2013**, *16*, 379–389. [CrossRef]
82. Miyata, T.; Kodama, T.; Honma, R.; Nezu, Y.; Harada, Y.; Yogo, T.; Hara, Y.; Tagawa, M. Influence of General Anesthesia with Isoflurane Following Propofol-Induction on Natural Killer Cell Cytotoxic Activities of Peripheral Blood Lymphocytes in Dogs. *J. Vet. Med. Sci.* **2013**, *75*, 917–921. [CrossRef] [PubMed]
83. Jun, I.-J.; Jo, J.-Y.; Kim, J.-I.; Chin, J.-H.; Kim, W.-J.; Kim, H.R.; Lee, E.-H.; Choi, I.-C. Impact of Anesthetic Agents on Overall and Recurrence-Free Survival in Patients Undergoing Esophageal Cancer Surgery: A Retrospective Observational Study. *Sci. Rep.* **2017**, *7*, 14020. [CrossRef] [PubMed]
84. Wigmore, T.J.; Jhanji, S. Long-Term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery. Retrospective Analysis. *Anesthesiology* **2016**, *124*, 69–79. [CrossRef] [PubMed]
85. Lascelles, B.D.X.; Kirkby Shaw, K. An Extended Release Local Anaesthetic: Potential for Future Use in Veterinary Surgical Patients? *Vet. Med. Sci.* **2016**, *2*, 229–238. [CrossRef] [PubMed]
86. Romano, M.; Portela, D.A.; Breghi, G.; Otero, P.E. Stress-Related Biomarkers in Dogs Administered Regional Anaesthesia or Fentanyl for Analgesia during Stifle Surgery. *Vet. Anaesth. Analg.* **2016**, *43*, 44–54. [CrossRef]
87. Grubb, T.; Lobprise, H. Local and Regional Anaesthesia in Dogs and Cats: Overview of Concepts and Drugs (Part 1). *Vet. Med. Sci.* **2020**, *6*, 209–217. [CrossRef]
88. Gargiulo, S.; Greco, A.; Gramanzini, M.; Esposito, S.; Affuso, A.; Brunetti, A.; Vesce, G. Mice Anesthesia, Analgesia, and Care, Part I: Anesthetic Considerations in Preclinical Research. *ILAR J.* **2012**, *53*, E55–E69. [CrossRef]
89. Mahmoud, K.; Ammar, A. Immunomodulatory Effects of Anesthetics during Thoracic Surgery. *Anesthesiol. Res. Pract.* **2011**, *2011*, 317410. [CrossRef]
90. Mitsuhata, H.; Shimizu, R.; Yokoyama, M.M. Suppressive Effects of Volatile Anesthetics on Cytokine Release in Human Peripheral Blood Mononuclear Cells. *Int. J. Immunopharmacol.* **1995**, *17*, 529–534. [CrossRef]
91. Melamed, R.; Bar-Yosef, S.; Shakhar, G.; Shakhar, K.; Ben-Eliyahu, S. Suppression of Natural Killer Cell Activity and Promotion of Tumor Metastasis by Ketamine, Thiopental, and Halothane, but Not by Propofol: Mediating Mechanisms and Prophylactic Measures. *Anesth. Analg.* **2003**, *97*, 1331–1339. [CrossRef]
92. Huang, H.; Benzonana, L.L.; Zhao, H.; Watts, H.R.; Perry, N.J.S.; Bevan, C.; Brown, R.; Ma, D. Prostate Cancer Cell Malignancy via Modulation of HIF-1α Pathway with Isoflurane and Propofol Alone and in Combination. *Br. J. Cancer* **2014**, *111*, 1338–1349. [CrossRef]
93. Deng, X.; Vipani, M.; Liang, G.; Gouda, D.; Wang, B.; Wei, H. Sevoflurane Modulates Breast Cancer Cell Survival via Modulation of Intracellular Calcium Homeostasis. *BMC Anesth.* **2020**, *20*, 253. [CrossRef]
94. Zhang, W.; Shao, X. Isoflurane Promotes Non-Small Cell Lung Cancer Malignancy by Activating the Akt-Mammalian Target of Rapamycin (mTOR) Signaling Pathway. *Med. Sci. Monit.* **2016**, *22*, 4644–4650. [CrossRef]
95. Boost, K.A.; Flondor, M.; Hofstetter, C.; Platacis, I.; Stegewerth, K.; Hoegl, S.; Nguyen, T.; Muhl, H.; Zwissler, B. The Beta-Adrenoceptor Antagonist Propranolol Counteracts Anti-Inflammatory Effects of Isoflurane in Rat Endotoxemia. *Acta Anaesthesiol. Scand.* **2007**, *51*, 900–908. [CrossRef] [PubMed]
96. Seymour, C.; Gleed, R.; British Small Animal Veterinary Association. *BSAVA Manual of Small Animal Anaesthesia and Analgesia*, 2nd ed.; BSAVA: Gloucester, UK, 1999.
97. Brand, J.-M.; Kirchner, H.; Poppe, C.; Schmucker, P. The Effects of General Anesthesia on Human Peripheral Immune Cell Distribution and Cytokine Production. *Clin. Immunol. Immunopathol.* **1997**, *83*, 190–194. [CrossRef]

98. Wei, H.; Sun, T.; Liu, J.; Wang, X.; Zhao, G.; Shi, J.; Chen, Y. Isoflurane Activates AMP-Activated Protein Kinase to Inhibit Proliferation, and Promote Apoptosis and Autophagy in Cervical Carcinoma Both in vitro and in vivo. *J. Recept. Signal Transduct.* **2021**, *41*, 538–545. [CrossRef]
99. Markovic, S.N.; Murasko, D.M. Inhibition of Induction of Natural Killer Activity in Mice by General Anesthesia (Avertin): Role of Interferon. *Clin. Immunol. Immunopathol.* **1991**, *60*, 181–189. [CrossRef]
100. Inada, T.; Yamanouchi, Y.; Jomura, S.; Sakamoto, S.; Takahashi, M.; Kambara, T.; Shingu, K. Effect of Propofol and Isoflurane Anaesthesia on the Immune Response to Surgery. *Anaesthesia* **2004**, *59*, 954–959. [CrossRef] [PubMed]
101. Faller, S.; Strosing, K.M.; Ryter, S.W.; Buerkle, H.; Loop, T.; Schmidt, R.; Hoetzel, A. The Volatile Anesthetic Isoflurane Prevents Ventilator-Induced Lung Injury via Phosphoinositide 3-Kinase/Akt Signaling in Mice. *Anesth. Analg.* **2012**, *114*, 747–756. [CrossRef] [PubMed]
102. Dolcet, X.; Llobet, D.; Pallares, J.; Matias-Guiu, X. NF-kB in Development and Progression of Human Cancer. *Virchows Arch.* **2005**, *446*, 475–482. [CrossRef]
103. Kawaraguchi, Y.; Horikawa, Y.T.; Murphy, A.N.; Murray, F.; Miyanohara, A.; Ali, S.S.; Head, B.P.; Patel, P.M.; Roth, D.M.; Patel, H.H. Volatile Anesthetics Protect Cancer Cells against Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand-Induced Apoptosis via Caveolins. *Anesthesiology* **2011**, *115*, 499–508. [CrossRef]
104. Benzonana, L.L.; Perry, N.J.S.; Watts, H.R.; Yang, B.; Perry, I.A.; Coombes, C.; Takata, M.; 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* **2013**, *119*, 593–605. [CrossRef] [PubMed]
105. Zhu, M.; Li, M.; Zhou, Y.; Dangelmajer, S.; Kahlert, U.D.; Xie, R.; Xi, Q.; Shahveranov, A.; Ye, D.; Lei, T. Isoflurane Enhances the Malignant Potential of Glioblastoma Stem Cells by Promoting Their Viability, Mobility in Vitro and Migratory Capacity in Vivo. *Br. J. Anaesth.* **2016**, *116*, 870–877. [CrossRef] [PubMed]
106. Luo, X.; Zhao, H.; Hennah, L.; Ning, J.; Liu, J.; Tu, H.; Ma, D. Impact of Isoflurane on Malignant Capability of Ovarian Cancer in vitro. *Br. J. Anaesth.* **2015**, *114*, 831–839. [CrossRef] [PubMed]
107. Minguet, G.; Franck, T.; Joris, J.; Ceusters, J.; Mouithys-Mickalad, A.; Serteyn, D.; Sandersen, C. Effects of Isoflurane and Sevoflurane on the Neutrophil Myeloperoxidase System of Horses. *Vet. Immunol. Immunopathol.* **2015**, *165*, 93–97. [CrossRef] [PubMed]
108. Prokopowicz, Z.; Marcinkiewicz, J.; Katz, D.R.; Chain, B.M. Neutrophil Myeloperoxidase: Soldier and Statesman. *Arch. Immunol. Ther. Exp.* **2012**, *60*, 43–54. [CrossRef]
109. Meier, A.; Gross, E.T.E.; Schilling, J.M.; Seelige, R.; Jung, Y.; Santosa, E.; Searles, S.; Lin, T.; Tu, X.M.; Patel, H.H.; et al. Isoflurane Impacts Murine Melanoma Growth in a Sex-Specific, Immune-Dependent Manner: A Brief Report. *Anesth. Analg.* **2018**, *126*, 1910–1913. [CrossRef]
110. Tyther, R.; O'Brien, J.; Wang, J.; Redmond, H.P.; Shorten, G. Effect of Sevoflurane on Human Neutrophil Apoptosis. *Eur. J. Anaesthesiol.* **2005**, *20*, 111–115. [CrossRef]
111. Tyther, R.; Fanning, N.; Halligan, M.; Wang, J.; Redmond, H.P.; Shorten, G. The Effect of the Anaesthetic Agent Isoflurane on the Rate of Neutrophil Apoptosis in vitro. *Ir. J. Med. Sci.* **2001**, *170*, 41. [CrossRef]
112. Morisaki, H.; Aoyama, Y.; Shimada, M.; Ochiai, R.; Takeda, J. Leucocyte Distribution during Sevoflurane Anaesthesia. *Br. J. Anaesth.* **1998**, *80*, 502–503. [CrossRef]
113. Loop, T.; Dovi-Akue, D.; Frick, M.; Roesslein, M.; Egger, L.; Humar, M.; Hoetzel, A.; Schmidt, R.; Borner, C.; Pahl, H.L.; et al. Volatile Anesthetics Induce Caspase-Dependent, Mitochondria-Mediated Apoptosis in Human T Lymphocytes in vitro. *Anesthesiology* **2005**, *102*, 1147–1157. [CrossRef] [PubMed]
114. Levins, K.J.; Prendeville, S.; Conlon, S.; Buggy, D.J. The Effect of Anesthetic Technique on M-Opioid Receptor Expression and Immune Cell Infiltration in Breast Cancer. *J. Anesth.* **2018**, *32*, 792–796. [CrossRef] [PubMed]
115. Elena, G.; Amerio, N.; Ferrero, P.; Bay, M.L.; Valenti, J.; Colucci, D.; Puig, N.R. Effects of Repetitive Sevoflurane Anaesthesia on Immune Response, Select Biochemical Parameters and Organ Histology in Mice. *Lab. Anim.* **2003**, *37*, 193–203. [CrossRef]
116. Wei, H.; Liang, G.; Yang, H.; Wang, Q.; Hawkins, B.; Madesh, M.; Wang, S.; Eckenhoff, R.G. The Common Inhalational Anesthetic Isoflurane Induces Apoptosis via Activation of Inositol 1,4,5-Trisphosphate Receptors. *Anesthesiology* **2008**, *108*, 251–260. [CrossRef] [PubMed]
117. Beck-Schimmer, B.; Baumann, L.; Restin, T.; Eugster, P.; Hasler, M.; Booy, C.; Schläpfer, M. Sevoflurane Attenuates Systemic Inflammation Compared with Propofol, but Does Not Modulate Neuro-Inflammation: A Laboratory Rat Study. *Eur. J. Anaesthesiol.* **2017**, *34*, 764–775. [CrossRef] [PubMed]
118. Tavare, A.N.; Perry, N.J.S.; Benzonana, L.L.; Takata, M.; Ma, D. Cancer Recurrence after Surgery: Direct and Indirect Effects of Anesthetic Agents*. *Int. J. Cancer* **2012**, *130*, 1237–1250. [CrossRef] [PubMed]
119. Gao, K.; Su, Z.; Liu, H.; Liu, Y. Retraction Notice to "Anti-Proliferation and Anti-Metastatic Effects of Sevoflurane on Human Osteosarcoma U2OS and Saos-2 Cells" [Experimental and Molecular Pathology 108 (2019) 121–130]. *Exp. Mol. Pathol.* **2022**, *127*, 104784. [CrossRef] [PubMed]
120. Kurosawa, S. Anesthesia in Patients with Cancer Disorders. *Curr. Opin. Anaesthesiol.* **2012**, *25*, 376–384. [CrossRef] [PubMed]
121. Wada, H.; Seki, S.; Takahashi, T.; Kawarabayashi, N.; Higuchi, H.; Habu, Y.; Sugahara, S.; Kazama, T. Combined Spinal and General Anesthesia Attenuates Liver Metastasis by Preserving Th1/Th2 Cytokine Balance. *Anesthesiology* **2007**, *106*, 499–506. [CrossRef]

122. Ishikawa, M.; Tanaka, S.; Arai, M.; Genda, Y.; Sakamoto, A. Differences in microRNA Changes of Healthy Rat Liver between Sevoflurane and Propofol Anesthesia. *Anesthesiology* **2012**, *117*, 1245–1252. [CrossRef]
123. Ali Syeda, Z.; Langden, S.S.S.; Munkhzul, C.; Lee, M.; Song, S.J. Regulatory Mechanism of MicroRNA Expression in Cancer. *Int. J. Mol. Sci.* **2020**, *21*, 1723. [CrossRef] [PubMed]
124. Nesek Adam, V.; Marin, D.; Popović, M.; Berić Lerotić, S.; Gudan Kurilj, A.; Matičić, D.; Vnuk, D. The Effect of Repeated Sevoflurane and Nitrous Oxide Exposure on Immunity in Rabbits. *Vet. Arh.* **2018**, *88*, 37–48. [CrossRef]
125. Argano, M.; De Maria, R.; Vogl, C.; Rodlsberger, K.; Buracco, P.; Larenza Menzies, M.P. Canine Mammary Tumour Cells Exposure to Sevoflurane: Effects on Cell Proliferation and Neuroepithelial Transforming Gene 1 Expression. *Vet. Anaesth. Analg.* **2019**, *46*, 369–374. [CrossRef] [PubMed]
126. Cattai, A.; Rabozzi, R.; Ferasin, H.; Isola, M.; Franci, P. Haemodynamic Changes during Propofol Induction in Dogs: New Findings and Approach of Monitoring. *BMC Vet. Res.* **2018**, *14*, 282. [CrossRef]
127. Kato, K.; Itami, T.; Nomoto, K.; Endo, Y.; Tamura, J.; Oyama, N.; Sano, T.; Yamashita, K. The Anesthetic Effects of Intramuscular Alfaxalone in Dogs Premedicated with Low-Dose Medetomidine and/or Butorphanol. *J. Vet. Med. Sci.* **2021**, *83*, 53–61. [CrossRef]
128. Lee, M.; Kim, S.; Moon, C.; Park, J.; Lee, H.; Jeong, S.M. Anesthetic Effect of Different Ratio of Ketamine and Propofol in Dogs. *J. Vet. Clin.* **2017**, *34*, 234–240. [CrossRef]
129. Ilkiw, J.E. Balanced Anesthetic Techniques in Dogs and Cats. *Clin. Tech. Small Anim. Pract.* **1999**, *14*, 27–37. [CrossRef]
130. Eden, C.; Esses, G.; Katz, D.; DeMaria, S. Effects of Anesthetic Interventions on Breast Cancer Behavior, Cancer-Related Patient Outcomes, and Postoperative Recovery. *Surg. Oncol.* **2018**, *27*, 266–274. [CrossRef]
131. Barr, C.A.; Alvarado, F.; Chang, Y.-M.; Luo, J.; Garden, O.A. The Impact of Alfaxalone, Propofol and Ketamine on Canine Peripheral Blood Lymphocyte Cytotoxicity in vitro. *Res. Vet. Sci.* **2021**, *136*, 182–184. [CrossRef]
132. Li, C.; Xia, M.; Wang, H.; Li, W.; Peng, J.; Jiang, H. Propofol Facilitates Migration and Invasion of Oral Squamous Cell Carcinoma Cells by Upregulating SNAI1 Expression. *Life Sci.* **2020**, *241*, 117143. [CrossRef]
133. Meng, C.; Song, L.; Wang, J.; Li, D.; Liu, Y.; Cui, X. Propofol Induces Proliferation Partially via Downregulation of P53 Protein and Promotes Migration via Activation of the Nrf2 Pathway in Human Breast Cancer Cell Line MDA-MB-231. *Oncol. Rep.* **2017**, *37*, 841–848. [CrossRef]
134. Feng, C.; Qian, D.; Chen, C. A Meta-Analysis and Systematic Review of Propofol on Liver Ischemia-Reperfusion Injury Protection during Hepatocellular Carcinoma Anesthesia Surgery. *Ann. Palliat. Med.* **2021**, *10*, 6726–6735. [CrossRef] [PubMed]
135. Cai, J.; Hu, Y.; Li, W.; Li, L.; Li, S.; Zhang, M.; Li, Q. The Neuroprotective Effect of Propofol against Brain Ischemia Mediated by the Glutamatergic Signaling Pathway in Rats. *Neurochem. Res.* **2011**, *36*, 1724–1731. [CrossRef] [PubMed]
136. Wang, H.; Wang, G.; Yu, Y.; Wang, Y. The Role of Phosphoinositide-3-Kinase/Akt Pathway in Propofol-Induced Postconditioning against Focal Cerebral Ischemia-Reperfusion Injury in Rats. *Brain Res.* **2009**, *1297*, 177–184. [CrossRef]
137. Kubo, K.; Inada, T.; Shingu, K. Possible Role of Propofol's Cyclooxygenase-Inhibiting Property in Alleviating Dopaminergic Neuronal Loss in the Substantia Nigra in an MPTP-Induced Murine Model of Parkinson's Disease. *Brain Res.* **2011**, *1387*, 125–133. [CrossRef]
138. Nyssen, P.; Franck, T.; Serteyn, D.; Mouithys-Mickalad, A.; Hoebeke, M. Propofol Metabolites and Derivatives Inhibit the Oxidant Activities of Neutrophils and Myeloperoxidase. *Free Radic. Biol. Med.* **2022**, *191*, 164–175. [CrossRef]
139. Jiang, S.; Liu, Y.; Huang, L.; Zhang, F.; Kang, R. Effects of Propofol on Cancer Development and Chemotherapy: Potential Mechanisms. *Eur. J. Pharmacol.* **2018**, *831*, 46–51. [CrossRef]
140. Ma, X.; Wang, T.; Zhao, Z.-L.; Jiang, Y.; Ye, S. Propofol Suppresses Proinflammatory Cytokine Production by Increasing ABCA1 Expression via Mediation by the Long Noncoding RNA LOC286367. *Mediat. Inflamm.* **2018**, *2018*, 8907143. [CrossRef]
141. Li, X.; Li, L.; Liang, F.; Liu, G.; Zhao, G. Anesthetic Drug Propofol Inhibits the Expression of Interleukin-6, Interleukin-8 and Cyclooxygenase-2, a Potential Mechanism for Propofol in Suppressing Tumor Development and Metastasis. *Oncol. Lett.* **2018**, *15*, 9523–9528. [CrossRef]
142. Xu, Y.; Jiang, W.; Xie, S.; Xue, F.; Zhu, X. The Role of Inhaled Anesthetics in Tumorigenesis and Tumor Immunity. *Cancer Manag. Res.* **2020**, *12*, 1601–1609. [CrossRef]
143. Sen, Y.; Xiyang, H.; Yu, H. Effect of Thoracic Paraspinal Block-Propofol Intravenous General Anesthesia on VEGF and TGF-β in Patients Receiving Radical Resection of Lung Cancer. *Medicine* **2019**, *98*, e18088. [CrossRef] [PubMed]
144. Pirttikangas, C.-O.; Salo, M.; Mansikka, M.; Grönroos, J.; Pulkki, K.; Peltola, O. The Influence of Anaesthetic Technique upon the Immune Response to Hysterectomy: A Comparison of Propofol Infusion and Isoflurane. *Anaesthesia* **1995**, *50*, 1056–1061. [CrossRef]
145. Yamada, R.; Tsuchida, S.; Hara, Y.; Tagawa, M.; Ogawa, R. Apoptotic Lymphocytes Induced by Surgical Trauma in Dogs. *J. Anesth.* **2002**, *16*, 131–137. [CrossRef]
146. Faroni, E.; Sabattini, S.; Lenzi, J.; Guerra, D.; Comazzi, S.; Aresu, L.; Mazzanti, A.; Zanardi, S.; Cola, V.; Lotito, E.; et al. Sleeping Beauty: Anesthesia May Promote Relapse in Dogs with Diffuse Large B-Cell Lymphoma in Complete Remission After Chemo-Immunotherapy. *Front. Vet. Sci.* **2021**, *8*, 760603. [CrossRef]
147. Inada, T.; Kubo, K.; Shingu, K. Promotion of Interferon-Gamma Production by Natural Killer Cells via Suppression of Murine Peritoneal Macrophage Prostaglandin E2 Production Using Intravenous Anesthetic Propofol. *Int. Immunopharmacol.* **2010**, *10*, 1200–1208. [CrossRef]

148. Kambara, T.; Inada, T.; Kubo, K.; Shingu, K. Propofol Suppresses Prostaglandin E_2 Production in Human Peripheral Monocytes. *Immunopharmacol. Immunotoxicol.* **2009**, *31*, 117–126. [CrossRef] [PubMed]
149. Kushida, A.; Inada, T.; Shingu, K. Enhancement of Antitumor Immunity after Propofol Treatment in Mice. *Immunopharmacol. Immunotoxicol.* **2007**, *29*, 477–486. [CrossRef]
150. Hiller, J.G.; Perry, N.J.; Poulogiannis, G.; Riedel, B.; Sloan, E.K. Perioperative Events Influence Cancer Recurrence Risk after Surgery. *Nat. Rev. Clin. Oncol.* **2018**, *15*, 205–218. [CrossRef]
151. Mao, L.; Lin, S.; Lin, J. The Effects of Anesthetics on Tumor Progression. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2013**, *5*, 1–10.
152. Cui, C.; Zhang, D.; Sun, K.; Zhu, Y.; Xu, J.; Kang, Y.; Zhang, G.; Cai, Y.; Mao, S.; Long, R.; et al. Propofol Maintains Th17/Treg Cell Balance in Elderly Patients Undergoing Lung Cancer Surgery through GABAA Receptor. *BMC Immunol.* **2022**, *23*, 58. [CrossRef] [PubMed]
153. Knochelmann, H.M.; Dwyer, C.J.; Bailey, S.R.; Amaya, S.M.; Elston, D.M.; Mazza-McCrann, J.M.; Paulos, C.M. When Worlds Collide: Th17 and Treg Cells in Cancer and Autoimmunity. *Cell Mol. Immunol.* **2018**, *15*, 458–469. [CrossRef] [PubMed]
154. Blanco, M.J.; Moreno-Bueno, G.; Sarrio, D.; Locascio, A.; Cano, A.; Palacios, J.; Nieto, M.A. Correlation of Snail Expression with Histological Grade and Lymph Node Status in Breast Carcinomas. *Oncogene* **2002**, *21*, 3241–3246. [CrossRef]
155. Nimmo, A.F.; Absalom, A.R.; Bagshaw, O.; Biswas, A.; Cook, T.M.; Costello, A.; Grimes, S.; Mulvey, D.; Shinde, S.; Whitehouse, T.; et al. Guidelines for the Safe Practice of Total Intravenous Anaesthesia (TIVA): Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia. *Anaesthesia* **2019**, *74*, 211–224. [CrossRef] [PubMed]
156. Bustamante, R.; Canfrán, S.; Gómez de Segura, I.A.; Aguado, D. Intraoperative Effect of Low Doses of Ketamine or Dexmedetomidine Continuous Rate Infusions in Healthy Dogs Receiving Propofol Total Intravenous Anaesthesia and Epidural Anaesthesia: A Prospective, Randomised Clinical Study. *Res. Vet. Sci.* **2022**, *143*, 4–12. [CrossRef]
157. Nolan, A.; Reid, J. Pharmacokinetics of Propofol Administered by Infusion in Dogs Undergoing Surgery. *Br. J. Anaesth.* **1993**, *70*, 546–551. [CrossRef]
158. Guzel, O.; Sevim, G.; Aydin Kaya, D.; Sezer, D.; Erek, M.; Esen Gursel, F.; Atmaca, G.; Demirtas, B.; Matur, E. Ketamine or Propofol Anesthesia in Dogs: How Do They Affect Cytokines, Antioxidants and Neutrophil Functions? *J. Hell. Vet. Med. Soc.* **2022**, *73*, 3783–3792. [CrossRef]
159. Schneemilch, C.E.; Ittenson, A.; Ansorge, S.; Hachenberg, T.; Bank, U. Effect of 2 Anesthetic Techniques on the Postoperative Proinflammatory and Anti-Inflammatory Cytokine Response and Cellular Immune Function to Minor Surgery. *J. Clin. Anesth.* **2005**, *17*, 517–527. [CrossRef]
160. Chang, C.-Y.; Wu, M.-Y.; Chien, Y.-J.; Su, I.-M.; Wang, S.-C.; Kao, M.-C. Anesthesia and Long-Term Oncological Outcomes: A Systematic Review and Meta-Analysis. *Anesth. Analg.* **2021**, *132*, 623–634. [CrossRef]
161. Ferré, P.J.; Pasloske, K.; Whittem, T.; Ranasinghe, M.G.; Li, Q.; Lefebvre, H.P. Plasma Pharmacokinetics of Alfaxalone in Dogs after an Intravenous Bolus of Alfaxan-CD RTU. *Vet. Anaesth. Analg.* **2006**, *33*, 229–236. [CrossRef]
162. Murison, P.J.; Taboada, F.M. Effect of Propofol and Alfaxalone on Pain after Ovariohysterectomy in Cats. *Vet. Rec.* **2010**, *166*, 334–335. [CrossRef]
163. Mathis, A.; Pinelas, R.; Brodbelt, D.C.; Alibhai, H.I. Comparison of Quality of Recovery from Anaesthesia in Cats Induced with Propofol or Alfaxalone. *Vet. Anaesth. Analg.* **2012**, *39*, 282–290. [CrossRef] [PubMed]
164. Jiménez, C.P.; Mathis, A.; Mora, S.S.; Brodbelt, D.; Alibhai, H. Evaluation of the Quality of the Recovery after Administration of Propofol or Alfaxalone for Induction of Anaesthesia in Dogs Anaesthetized for Magnetic Resonance Imaging. *Vet. Anaesth. Analg.* **2012**, *39*, 151–159. [CrossRef] [PubMed]
165. Sun, H.; Zheng, X.; Zhou, Y.; Zhu, W.; Ou, Y.; Shu, M.; Gao, X.; Leng, T.; Qiu, P.; Yan, G. Alphaxalone Inhibits Growth, Migration and Invasion of Rat C6 Malignant Glioma Cells. *Steroids* **2013**, *78*, 1041–1045. [CrossRef]
166. Suzuki, T.; Tomioka, M.; Uchida, M.K. Inhibitory Effects of Steroidal Anesthetics on Histamine Release from Rat Mast Cells Stimulated by Concanavalin A, Compound 48/80 and A23187. *Gen. Pharmacol. Vasc. Syst.* **1988**, *19*, 435–440. [CrossRef] [PubMed]
167. Sheehy, K.A.; Lippold, C.; Rice, A.L.; Nobrega, R.; Finkel, J.C.; Quezado, Z.M. Subanesthetic Ketamine for Pain Management in Hospitalized Children, Adolescents, and Young Adults: A Single-Center Cohort Study. *J. Pain Res.* **2017**, *10*, 787–795. [CrossRef] [PubMed]
168. Lilius, T.O.; Jokinen, V.; Neuvonen, M.S.; Niemi, M.; Kalso, E.A.; Rauhala, P.V. Ketamine Coadministration Attenuates Morphine Tolerance and Leads to Increased Brain Concentrations of Both Drugs in the Rat. *Br. J. Pharmacol.* **2015**, *172*, 2799–2813. [CrossRef] [PubMed]
169. Loix, S.; De Kock, M.; Henin, P. The Anti-Inflammatory Effects of Ketamine: State of the Art. *Acta Anaesthesiol. Belg.* **2011**, *62*, 47–58.
170. Spencer, H.F.; Berman, R.Y.; Boese, M.; Zhang, M.; Kim, S.Y.; Radford, K.D.; Choi, K.H. Effects of an Intravenous Ketamine Infusion on Inflammatory Cytokine Levels in Male and Female Sprague–Dawley Rats. *J. Neuroinflamm.* **2022**, *19*, 75. [CrossRef]
171. Lu, W.; Wang, L.; Wo, C.; Yao, J. Ketamine Attenuates Osteoarthritis of the Knee via Modulation of Inflammatory Responses in a Rabbit Model. *Mol. Med. Rep.* **2016**, *13*, 5013–5020. [CrossRef]
172. Brinck, E.; Tiippana, E.; Heesen, M.; Bell, R.F.; Straube, S.; Moore, R.A.; Kontinen, V. Perioperative Intravenous Ketamine for Acute Postoperative Pain in Adults. *Cochrane Database Syst. Rev.* **2018**, *68*, 110071. [CrossRef]
173. Plein, L.M.; Rittner, H.L. Opioids and the Immune System—Friend or Foe. *Br. J. Pharmacol.* **2018**, *175*, 2717–2725. [CrossRef]

174. Hardy, J.; Quinn, S.; Fazekas, B.; Plummer, J.; Eckermann, S.; Agar, M.; Spruyt, O.; Rowett, D.; Currow, D.C. Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain. *J. Clin. Oncol.* **2012**, *30*, 3611–3617. [CrossRef] [PubMed]
175. Lankveld, D.P.K.; Bull, S.; Van Dijk, P.; Fink-Gremmels, J.; Hellebrekers, L.J. Ketamine Inhibits LPS-Induced Tumour Necrosis Factor-Alpha and Interleukin-6 in an Equine Macrophage Cell Line. *Vet. Res.* **2005**, *36*, 257–262. [CrossRef] [PubMed]
176. Ohta, N.; Ohashi, Y.; Fujino, Y. Ketamine Inhibits Maturation of Bone Marrow-Derived Dendritic Cells and Priming of the Th1-Type Immune Response. *Anesth. Analg.* **2009**, *109*, 793–800. [CrossRef] [PubMed]
177. Beilin, B.; Rusabrov, Y.; Shapira, Y.; Roytblat, L.; Greemberg, L.; Yardeni, I.Z.; Bessler, H. Low-Dose Ketamine Affects Immune Responses in Humans during the Early Postoperative Period. *Br. J. Anaesth.* **2007**, *99*, 522–527. [CrossRef]
178. Braun, S.; Gaza, N.; Werdehausen, R.; Hermanns, H.; Bauer, I.; Durieux, M.E.; Hollmann, M.W.; Stevens, M.F. Ketamine Induces Apoptosis via the Mitochondrial Pathway in Human Lymphocytes and Neuronal Cells. *Br. J. Anaesth.* **2010**, *105*, 347–354. [CrossRef]
179. Hirota, K.; Lambert, D.G. Ketamine: New Uses for an Old Drug? *Br. J. Anaesth.* **2011**, *107*, 123–126. [CrossRef]
180. Laudanski, K.; Qing, M.; Oszkiel, H.; Zawadka, M.; Lapko, N.; Nowak, Z.; Worthen, G.S. Ketamine Affects In Vitro Differentiation of Monocyte into Immature Dendritic Cells. *Anesthesiology* **2015**, *123*, 628–641. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.