Review

Drugs of anaesthesia and cancer

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KEYWORDS
Anesthesia; anesthetics; cancer; complications; effects; general anesthetics; intravenous anesthetics; nitrous oxide; opioids; neuromuscular blocking drugs; oncology; regional anesthesia; risk; volatile anesthetics

Abstract
Anaesthesia represents one of the most important medical advances in history, and, nowadays, can widely be considered safe, thanks to the discovery of new drugs and the adoption of modern technologies. Nevertheless, anaesthetic practices still represent cause for concern regarding the consequences they produce. Various anaesthetics are frequently used without knowing their effects on specific diseases: despite having been reported that invasion or metastasis of cancer cells easily occurs during surgical procedures, numerous anaesthetics are used for cancer resection even if their effect on the behaviour of cancer cells is unclear.

Guidelines for a proper use of anaesthetics in cancer surgery are not available, therefore, the aim of the present review is to survey available up-to-date information on the effects of the most used drugs in anaesthesia (volatile and intravenous anaesthetics, nitrous oxide, opioids, local anaesthetics and neuromuscular blocking drugs) in correlation to cancer. This kind of knowledge could be a basic valuable support to improve anaesthesia performance and patient safety.

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Introduction

Described as a group of diseases characterized by an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to spread, often resulting in death, cancer represents one of the most common causes of mortality in many countries around the world. The need for reliable risk calculation factors and prognostic criteria for tumours has been widely recognized, and many authors have attempted to define parameters to identify different factors involved in tumour genesis. Cancer is often treated by chemotherapy, immunotherapy, radiation and surgery. Anaesthesia has an important role in almost all of the above procedures, particularly during surgery. At present, many anaesthetic agents are used, during cancer resection surgery, for example, without knowing their effects on cancer, mutagenic potential, impaired metastatic capability, and growth of pre-existing tumour cells [1,2]. In spite of all of this, to date, few papers have been published specifically addressing a possible correlation between anaesthetic drugs and cancers, and the results are often confused and disputed. A comprehensive paper on interaction between anaesthetics and cancer is, therefore, timely.

In the staging of carcinogenesis, two phenomena have been proposed. One is malignant transformation, which is the result of a multi-step process in which cells acquire mutations of genes that activate protooncogenes or negate the action of tumour suppressor genes. The other phenomenon in carcinogenesis is immortalization [3]. First applied to cancer cells, the term immortalization describes the ability of cells to reproduce indefinitely: they escape from the normal limitation on growth of a finite number of division cycles (Hayflick limit).

Recently, it has been suggested that anaesthetic drugs can induce biomolecular change involved in different physiological and pathophysiological cellular functions, such as proliferation, angiogenesis and apoptosis [1,2,4]. These findings support the hypothesis that, by virtue of some still unknown mechanisms, anaesthesia regime may influence physiological cellular and/or molecular process, and that this is one possible explanation for their potential involvement in tumour development. Nevertheless, the possible role of anaesthetic drugs in cancer development and progression is still unclear.

The aim of the present review is to survey available up-to-date information on the effects of anaesthetic agents on cancer cells, in order to provide a useful means to decrease the risk of unwelcome events and to increase anaesthesia performance, patient safety and, in the future, maybe outcome. Moreover, this paper may be considered as a possible background for future studies designed to clarify the complex interactions between anaesthetic drugs and biomolecular pathways mainly involved in malignant tumour genesis.

Method

The evidence-based practice approach aims at incorporating the best available research evidence in clinical decision-making. It is a source of structured information that includes the following steps: asking answerable questions, accessing the best information, appraising information for validity and relevance, and applying information in patient care.

We formulated the following question: What are the effects on cancer of anaesthesia?

The structured question was used as a starting point for deriving search terms, as well as inclusion criteria for retrieving articles. More specifically, the name of each anaesthetic drug in combination with terms such as cancer, tumour, or cancer tumour has been used.

Owing to the medical nature of the question, the search was confined to three databases: The Cochrane Library, MedLine accessed through PubMed, and CINAHL.

Over one hundred and fifty articles — published from 1980 to 2008, and including studies in vitro, in animals and humans — were considered.

In the literature reviewed, there is evidence to support the fact that, by virtue of some still unknown mechanisms, anaesthesia regime may influence physiological cellular and/or molecular process involved in tumour development. Nevertheless, the possible role of anaesthetic drugs in cancer development and progression is still unclear.

Drugs of anaesthesia and cancer

"Volatile anaesthetic agents"

Used alone, or as part of a balanced anaesthesia, volatile anaesthetics have been the most usually given drugs in anaesthesia communities, for decades. Interaction between these drugs and cancer has been investigated...
[1,5], especially due to the suspect of inducing tumours, spontaneous abortions, and congenital anomalies, above all in chronically exposed anaesthetic staff [1]. These hypotheses, however, were not verified from the first animal and epidemiological studies on effects of chronic exposure to subaesthetic concentrations of volatile anaesthetic agents [6–8].

Halothane is a volatile anaesthetic which, even if replaced in many clinical practices by sevoflurane as it causes hepatocellular injury with a high mortality rate, is still widely employed in many countries and in several third world regions [9]. Halothane effects on cancer cells have also been extensively investigated. In 1986, Katsav et al. demonstrated how halothane, used during excision of Lewis lung carcinoma (3LL) tumour, decreases natural killer (NK) cell activity accelerating postsurgical metastasis growth of mouse tumours [10]. In 1994, Waxler et al., instead, investigated the effects of this volatile agent on tissue proteinase inhibitor content and tumour behaviour in lungs of mice. They demonstrated how the stimulation of proteinase inhibitory activity by halothane in oxygen may be responsible for the inhibition of tumour cell proliferation, resulting in smaller tumour nodules and with no effect on the incidence of colonization [11]. In more recent years, in their study in vitro on halothane, sevoflurane and isoflurane, Kvolik et al. have observed how, in the clinical setting, halothane has an antitumour potency which is higher in comparison to isoflurane [1]. In particular, growth suppression in cells exposed to halothane was enhanced in laryngeal carcinoma cells (HEP-2) (growth was reduced to 67.7% of the control amount), colon carcinoma cells (Caco-2) (to 76.3%), and poorly differentiated cells from lymph node metastasis of colon carcinoma (SW620) (to 80.9%), while it was minimal in normal fibroblasts (WI-38) (to 89.4%). Moreover, in Caco-2 cells treated by halothane, a decrease in deoxyribonucleic acid (DNA) synthesis (52.4%, p = 0.001), ribonucleic acid (RNA) synthesis (39.2%, p = 0.001), and protein synthesis (19.2%, p = 0.004) was recorded. In HEP-2 cells, DNA and RNA syntheses were decreased to 72.5% and 79.9%, whereas protein synthesis was 14% of controls. In SW620 cells, protein synthesis after 4 h was 24.4%, while a DNA fragmentation was observed in Caco-2 cells and pancreatic carcinoma cells (MIA PaCa-2) [1]. Also, the activity of NK cells was affected by halothane. Although its effect does not reach statistical significance, this drug, similarly to other anaesthetics (ketamine, thiopental), has been seen to reduce the number of circulating NK cells per millimetre of blood in rats, increasing lung metastases or MADB106 lung tumour retention (a selected variant cell line obtained from a pulmonary metastasis of a mammary adenocarcinoma — MADB100 — chemically induced in the inbred Fischer-344 rat) [4,12]. Nevertheless, the addition of spinal block to general halothane anaesthesia markedly attenuates (by 70%) the promotion of metastasis by surgery [13]. The effects of halothane on lung carcinoma cells A 549 have also been evaluated by Valtcheva et al., demonstrating that sub toxic halothane concentrations of 0.6 vol.% inhibit surfactant production; concentrations in the range of 0.8–1.4 vol.% induce membrane damage, and concentrations equal to and higher than 1.4 vol.% cell death of approximately 50% of the cells [14]. In rat glioma C6 cells, halothane inhibits the capacitive calcium ions (Ca$^{2+}$) influx with a 50% inhibitory concentration (IC50) of 1.9 vol.% [15], and, as demonstrated by other studies, halothane, at clinically relevant concentrations, inhibits Ca(2+)-ATPase (PMCA) pumping activity in a dose-dependent manner in cells of neural origin (rat C6 glioma cells, B104 rat neuroblastoma, PC12 rat pheochromocytoma) [16]. The effects of halothane based anaesthesia on K+ and carbachol stimulated [3H] noradrenaline release and associated increases in intracellular Ca$^{2+}$ in a cultured human neuroblastoma cell line, SH-SYSY, were investigated by Atcheson et al. [17]. The findings demonstrate how halothane produces a dose-dependent reduction in K+ evoked release of [3H] noradrenaline, with significant inhibition (17%) occurring from 1.26 atm%, a dose-dependent reduction in K+ evoked increases (measured at the peak) in intracellular Ca$^{2+}$ with significant inhibition (29%) occurring from 0.88 atm% [17]. In these kinds of cells, moreover, clinically relevant doses of halothane enhance basal and carbachol-stimulated second messenger inositol (1,4,5) triphosphate (Ins(1,4,5)P3) formation [18]. Basal and carbachol evoked release, instead, are not affected similarly to K+ plateau and basal carbachol evoked increases in intracellular Ca$^{2+}$ [17]. Finally, reversible suppression for activity of Hypoxia-inducible factor 1 (HIF-1), a central component in the hypoxic response pathway, has been observed by Tatsuya et al., in their study carried out using a cell line derived from a human hepatocellular carcinoma, Hep3B, and halothane, in a range of clinically relevant doses [3].

Isoflurane is an older inhalational anaesthetic, but is still widely used in clinical practice. Similar to sevoflurane, it modifies tumour cell growth in the time-dependent manner. Nevertheless, the inhibitory effect is absent or minimal in comparison to that recorded for other inhaled anaesthetics [1]. While isoflurane does not cause biologically important differences in tumour growth for either Caco-2 or MIA PaCa-2 cells, it shows an inhibitory effect after 6 h of exposure in normal fibroblasts WI-38. On HEP-2 cell lines, instead, it determines a slight increase in the growth of treated cells, while only a mild increase after 2 h of exposure, and changes lower than 5% are induced in metabolic activity, respectively, of MIA-Paca-2 and SW620 cells [1]. Moreover, according to the study in vitro by Mitsuhasha et al., isoflurane – in the same way as sevoflurane – is capable of altering the release of cytokines by NK and NK-like cells in response to tumour cells [19]. Unlike sevoflurane, instead, isoflurane seems to induce apoptosis rarely [1], even if it has been reported how clinically relevant concentrations of this anaesthetic induce apoptosis, alter amyloid precursor protein (APP) processing, and increase amyloid beta protein (Abeta) production in a human neuroglioma cell line [20,21]. Numerous other studies have been carried out on the interaction between this anaesthetic agent and cancer. Isoflurane seems to induce cytotoxicity in rat PC12 pheochromocytoma cells and primary cortical neurons, which may be related to its ability to decrease the ratio of apoptotic/antiapoptotic proteins Bcl-2/Bax, promoting apoptosis [22]. The effect of this anaesthetic on calcitonin gene-related peptide (CGRP), instead, was investigated by Kuroda et al., in their study on pithed rats and human neuroblastoma cells. The results suggest that isoflurane inhibits CGRP-induced
vasodilatation at the site between the CGRP receptor and adenylate cyclase activation, involving Gs protein [23]. Moreover, isoflurane enhances the expression and activity of glutamate transporter type 3 in C6 glioma cells [24]. In particular, it increases the expression and activity of excitatory amino acid transporter type 3 (EAAT3) by stabilizing EAAT3 mRNA and proteins via protein kinase C- and phosphatidylinositol 3 kinase-independent pathways [24]. Finally, it reported how xenon and isoflurane affect, lipodisaccharide (LPS)-induced activation of the nuclear transcription factor kB (NF-kB) in different ways [25]. While xenon increases, isoflurane inhibits the activation of NF-kB, highlighting a possible molecular mechanism for the different effects on monocyte tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) production [25]. In accordance with these results, Ke et al. have also demonstrated how, during open cholecystectomy, a total intravenous anaesthesia using propofol and remifentanil suppresses the inflammatory response caused by surgery to a greater extent than a balanced inhalation technique using isoflurane. The plasma levels of TNF-alpha, interleukin IL-6 and interleukin IL-10 — measured at the end of anaesthesia and surgery — are significantly higher when this anaesthetic agent is used [26] (Tables 1—3).

Sevoflurane is currently considered the inhalational agent of choice in anaesthesia. Its effects on Caco-2, Hep-2, MIA PaCa-2, SW-620 and WI-38 cells were investigated by Kvolik et al., simulating, in vitro, a clinical setting, where anaesthesia for cancer surgery usually takes a few hours [1]. The findings demonstrate how sevoflurane, similar to other inhaled anaesthetics, such as isoflurane and halothane, modifies tumour cell growth in a time-dependent manner [1]. In both Caco-2 and SW620 cells, for example, the growth of treated cells is significantly reduced after 6 h of exposure to sevoflurane. In Hep-2 cells, instead, sevoflurane favours cell growth in the first 2 h and then reduces it in a significant manner, while MIA PaCa-2 and WI-38 cells did not show marked growth alterations [1]. This inhalational anaesthetic is also capable of altering the release of cytokines by NK and NK-like cells in response to tumour cells, significantly inhibiting the release of interleukin-1 beta (IL-1 beta) and TNF-alpha, but not that of interleukin-2 (IL-2) [19].

In other words, sevoflurane expresses a marked inhibitory effect in most cell lines, which could represent a fundamental advantage when used in cancer surgery. Moreover, according to what Wada et al. found in their study on mice, the addition of spinal block to sevoflurane based anaesthesia accompanying surgery attenuates the suppression of tumoricidal function of liver mononuclear cells, presumably by preserving the T helper 1/T helper 2 (Th1/Th2) cytokine balance, thereby reducing the promotion of tumour metastasis [27].

In the context of the study described above, Kvolik and other authors demonstrated, nevertheless, how apoptosis can be detected in cells exposed to sevoflurane [1], while Wei et al., in their study on rats, showed how this volatile anaesthetic does not induce cytotoxicity in either PC12 cells or primary cortical neurons, leaving the Bcl-2/Bax ratio unchanged [22].

Desflurane, a recently introduced volatile anaesthetic drug, has a low blood/gas solubility coefficient that allows rapid changes in anaesthesia depth [28]. It is generally used in anaesthesia to facilitate rapid emergence. A faster recovery following desflurane, in fact, may be desirable especially after long surgical procedures, enabling the patient’s full cooperation and facilitating early diagnosis of any potential neurological deficit [29]. The effects of this drug on cancer have been poorly treated in literature.

“Intravenous anaesthetic agents”

Intravenous anaesthesia is a technique extensively administered in both surgical operations for cancer treatment and in the intensive care setting after surgery [2]. This use has focused the interest of research, for potential effects of the intravenous agents, on neoplastic tissue.

Propofol, a phenolic derivative, which is structurally unrelated to other sedative hypnotic agents, is an intravenous agent largely used for the induction of general anaesthesia in adult and paediatric patients older than 3 years of age; maintenance of general anaesthesia in adults, and children older than 2 months of age; and intensive care unit sedation for intubated, mechanically ventilated adults. Its pharmacokinetic profile is characterized by a rapid onset and short duration of action that, together with its stress control and amnesic properties, makes it an ideal hypnotic recommended during surgical procedures.

Different studies carried out have demonstrated how clinically relevant concentrations of propofol inhibit the invasion of human cancer cells by modulating RhoA [2]. In particular, it has been observed that in mice, a propofol infusion of 40 mg/kg per day, for 4 weeks, prevents pulmonary metastasis of cancer cells by inhibiting the invasion activity of cancer cells rather than by inhibiting their growth [2]. It should be emphasised that this animal model is not clinically relevant in terms of dosage and length of time administration. Nevertheless, these results confirm the study by Kushida et al., who found that this anaesthetic agent has a beneficial effect on antitumour immunity in mice [30]. Unlike other anaesthetics, propofol does not alter NK activity or increase MADB106 lung tumour retention or lung metastases [4]. The synthesis, purification, characterization and evaluation of two novel anticancer conjugates, propofol-docosahexaenoate (propofol-DHA) and propofol-eicosapentaenoate (propofol-EPA), are all described by Siddiqui et al. In particular, they demonstrate how these propofol based conjugates may be useful for the treatment of breast cancer. Although they are no longer considered anaesthetics, and therefore cannot be used as general anaesthesia, the propofol-DHA or propofol-EPA conjugates significantly inhibit cell adhesion (15—30%) and migration (about 50%) and induced apoptosis (about 40%) in breast cancer cells [31]. Different findings, instead, have been observed for MDA-MB-468 breast carcinoma cells that respond to non-volatile anaesthetics, such as propofol, with an increased migration. The activation of GABA-A receptors by propofol determines, in fact, that the migration of MDA-MB-468 cells (64.4 ± 7%) increases significantly to 85.0 ± 5.0% [32,33]. Moreover, while several studies of the effects of propofol on cytokine release from lipopolysaccharide (LPS) stimulated immune cells have produced conflicting findings demonstrating both inhibition and augmentation, Shibakawa et al. have investigated the

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Table 1 Summary of the most important effects of anaesthetic drugs on cancer in human studies.

<table>
<thead>
<tr>
<th>Anaesthetics</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>During open cholecystectomy, a TIVA with propofol and remifentanil suppresses the inflammatory response caused by surgery to a greater extent than a balanced inhalation technique using isoflurane: TNF-alpha, IL-6, IL-10 — measured at the end of anaesthesia and surgery — are significantly higher when isoflurane is used.</td>
<td>[31]</td>
</tr>
<tr>
<td>Propofol</td>
<td>During an open cholecystectomy a TIVA using propofol and remifentanil seems to suppress the inflammatory response caused by surgery to a greater extent than a balanced inhalation technique using isoflurane: the plasma levels of TNF-alpha, interleukin IL-6 and interleukin IL-10 — measured at the end of anaesthesia and surgery — are significantly lower in the propofol/remifentanil group than in the group treated with isoflurane.</td>
<td>[31]</td>
</tr>
<tr>
<td>Etomidate</td>
<td>A randomised controlled clinical trial have demonstrated how, in the critically ill single doses of this anaesthetic agent may interfere with cortisol synthesis, for at least 24 h.</td>
<td>[40]</td>
</tr>
<tr>
<td>Ketamine</td>
<td>The use of flow-dose ketamine — especially in women — may be beneficial for post-operative pain management after oral maxillofacial surgery, reducing the risk of cancer metastasis caused by suppressing NK cell activity.</td>
<td>[42]</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>Exposure to clinically-used concentrations of halothane and nitrous oxide does not interfere with the natural killer lymphocyte response in patients with benign and malignant breast disease. The administration of nitrous oxide to cancer-bearing patients, but not to those undergoing orthopaedic surgery, produces major changes in amino acid metabolism, and consideration should be given to the avoidance of exposure of cancer patients to nitrous oxide.</td>
<td>[62]</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Large dose fentanyl administration is more effective in suppression of immunity function than small-doses.</td>
<td>[77]</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Used in combination with propofol, it seems to suppress the inflammatory response caused by surgery. In ASA I-II patients undergoing simple abdominal hysterectomy, remifentanil-based anaesthesia, in combination with adequate analgesia, affects the natural killer cell count and increases neutrophils.</td>
<td>[31], [87]</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>TIVA with propofol and a minimal dose of sufentanil or a moderate dose midazolam-sufentanil affects the pro-inflammatory cytokine response to surgical stimulation before starting cardiopulmonary bypass, but it does not modify the pro-inflammatory cytokine response to ischemia-reperfusion or extracorporeal circulation. TIVA with propofol, sufentanil and atracurium does not affect IL-1beta, IL-4, IL-6, TNF-alpha and INF-gamma release in ASAI-II patients, undergoing elective laparoscopic or open cholecystectomy.</td>
<td>[93], [94]</td>
</tr>
<tr>
<td>Morphine</td>
<td>When administered in analgesic doses after surgery in cancer patients, does not affect NK cell activity that is, instead, significantly enhanced by tramadol administration. Humoral and cellular immunity is, in part, modulated by morphine-derived metabolites at the early phase of morphine therapy, in patients with advanced cancer who required morphine for pain relief.</td>
<td>[104], [111]</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Tramadol shows analgesic activity comparable to that of morphine, but induces improvement in postoperative immunosuppression suggesting how it may be preferred for the treatment of postoperative pain in cancer patients. The administration of this opioid before and after laparotomy seems to prevent surgery-induced NK activity suppression blocking the enhancement of lung metastases.</td>
<td>[104], [107], [118,119]</td>
</tr>
<tr>
<td>NMBDs</td>
<td>The effects of these drugs on cancer have been poorly investigated: the few existing studies have principally analyzed the influence of some of these agents on the proliferation of normal human cells and their pharmacokinetic and neuromuscular effects in patients with liver disease.</td>
<td></td>
</tr>
</tbody>
</table>
Table 2  Summary of the most important effects of anaesthetic drugs on cancer in animal studies.

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volatile Anaesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>Reduces NK cell activity accelerating postsurgical metastases growth of mouse tumours.</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>The stimulation of proteinase inhibitory activity by halothane in oxygen may be responsible for inhibition of tumour cell proliferation.</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>Reduces the number of NK cells per millimetre of blood, while it increases MADB106 lung tumour retention or lung metastases.</td>
<td>[4,20]</td>
</tr>
<tr>
<td></td>
<td>The addition of spinal block to general halothane anaesthesia attenuates (by 70%) the promotion of metastases by surgery.</td>
<td>[21]</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>The addition of spinal block to sevoflurane based anaesthesia attenuates (by 70%) the promotion of metastases by surgery.</td>
<td>[32]</td>
</tr>
<tr>
<td><strong>Intravenous Anaesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>It does not alter NK activity or increase MADB106 lung tumour retention or lung metastases.</td>
<td>[4]</td>
</tr>
<tr>
<td></td>
<td>The administration of this agent prevents oxidative stress, NF-kB activation and inducible nitric oxide synthase (iNOS) overexpression in liver rats. Therefore, propofol treatment might block the production of noxious mediators involved in the development of halothane-induced injury.</td>
<td>[18]</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Reduces the activity of NK cells and increases lung tumour retention and lung metastases more than 2.5 fold (effect markedly reduced when pre-treated with β-adrenergic antagonist — nadodol — or chronic small doses of an immunostimulator is executed).</td>
<td>[4]</td>
</tr>
<tr>
<td></td>
<td>Presents anti-inflammatory action in various immune cells (macrophage, peripheral leucocytes) stimulated with LPS in vitro and in vivo.</td>
<td>[43–45]</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Thiopental inhibits immune responses.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single dose of thiopental (37–42 mg/kg) — sufficient to achieve anaesthesia induction — increases the growth rate of a 3-methylcholanthrene-induced syngeneic murine fibrosarcoma in C57B1/6 mice with significant alterations in cell-mediated immunity.</td>
<td>[51–53]</td>
</tr>
<tr>
<td></td>
<td>Thiopental reduces NK activity significantly and increases MADB106 lung tumour retention or lung metastases: effect absent during excision of 3LL tumour, and aggravated by the presence of hypothermia during thiopental-based anaesthesia.</td>
<td>[4,14,54]</td>
</tr>
<tr>
<td><strong>Nitrous Oxide</strong></td>
<td>This agent, in low concentrations, is not responsible for the reportedly higher than average incidence of reticuloendothelial malignancies in operating room personnel.</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>During excision of the 3LL tumour in rats, the use of N2O has no effect on NK cell activity, avoiding postsurgical growth acceleration of metastases.</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>The use of this anaesthetic shortly before or during methotrexate administration — used in chemotherapeutic protocols for treatment of malignancies — should be avoided as it increases cytotoxic effects of methotrexate on proliferating cells with unexpected myelosuppression and mucosal damage.</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td>Combining the anticobalamin activity of N2O with an anti-folate seems to be a promising chemotherapeutic approach with significant anti-leukaemic potential.</td>
<td>[64]</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td>Fentanyl</td>
<td>Determines a consistent decrease of bone pain symptoms and tumour growth-induced bone destruction, showing clear antinociceptive properties, as well as reduction in cancer cell-induced bone lesions.</td>
</tr>
<tr>
<td></td>
<td>Used with intermediate doses, it suppresses NKCC, and increases MADB106 lung tumour retention in a correlated manner augmenting the risk of tumour metastases.</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>NKCC returns to control values in patients treated with small-dose fentanyl, whereas NKCC remains significantly suppressed after large-dose fentanyl administration.</td>
<td>[78,79]</td>
</tr>
<tr>
<td></td>
<td>Fentanyl does not prevent immunosuppression induced by surgery.</td>
<td>[73,79,80]</td>
</tr>
</tbody>
</table>
### Table 3 Summary of the most important effects of anaesthetic drugs on cancer for studies "in vitro".

<table>
<thead>
<tr>
<th>Anaesthetics</th>
<th>Effects</th>
<th>Cell Line</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volatile</strong></td>
<td>Halothane</td>
<td>Halothane has a higher antitumour potency than sevoflurane and isoflurane: growth suppression enhances in Hep-2, Caco-2 and SW620 cells, while it is minimal in WI-38 cells.</td>
<td>Hep-2, Caco-2, SW620, WI-38</td>
</tr>
<tr>
<td><strong>Anaesthetics</strong></td>
<td></td>
<td>The effects of halothane on lung carcinoma cells A 549 have also been evaluated demonstrating that sub toxic halothane concentrations of 0.6 vol.% inhibits surfactant production; concentrations in the range 0.8-1.4 vol.% induce membrane damage and concentrations ≥ 1.4 vol.%—cell death of approximately 50% of the cells.</td>
<td>A 549</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In rat glioma C6 cells it inhibits the capacitative Ca2+ influx with an IC50 of 1.9 %vol.</td>
<td>C6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Halothane, at clinically relevant concentrations, inhibits PMCA pumping in a dose-dependent manner in cells of neural origin (rat C6 glioma cells, B104 rat neuroblastoma, PC12 rat pheochromocytoma)</td>
<td>C6, B104, PC12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Produces a dose-dependent reduction in K+ evoked release of [3H]noradrenaline with significant inhibition, and a dose-dependent reduction in K+ evoked increases in intracellular Ca2+ with significant inhibition.</td>
<td>SH-SY5Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reversible suppression for activity of HIF-1 has been observed in a cell line derived from a human hepatocellular carcinoma, Hep3B, treated with halothane in a range of clinically relevant doses.</td>
<td>Hep3B</td>
</tr>
<tr>
<td><strong>Isoflurane</strong></td>
<td>Modifies tumour cell growth in a time dependent manner with inhibitory effect absent or minimal in comparison to other inhaled anaesthetics: in Caco-2 and Mia PaCa-2 cells it does not produce biologically important differences; in WI-38 cells shows an inhibitory effect after 6h of exposure; in Hep-2 cells a slight increase in growth of treated cells; in Mia PaCa-2 and SW620 cells induces changes &lt;5% in metabolic activity after 2h of exposure.</td>
<td>Hep-2, Caco-2, WI-38, MIA PaCa-2</td>
<td>[1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isoflurane seems to induce apoptosis rarely, even if clinically relevant concentration of isoflurane induces apoptosis, alters APP processing, and increases Abeta production in human neuroglioma cells.</td>
<td>[1,27,28]</td>
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<td></td>
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<td>Induces cytotoxicity in rat PC12 pheochromocytoma cells and primary cortical neurons.</td>
<td>PC12</td>
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<td>Isoflurane enhances the expression and activity of glutamate transporter type 3 in C6 glioma cells.</td>
<td>C6</td>
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<td></td>
<td></td>
<td>Isoflurane inhibits activation of the NF-kB.</td>
<td>[17]</td>
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<tr>
<td><strong>Sevoflurane</strong></td>
<td>Modifies tumour cell growth in a time dependent manner: in both Caco-2 and SW620 cells the growth of treated cells is significantly reduced after 6h of exposure to sevoflurane. In Hep-2 cells, instead, sevoflurane favours cell growth in the first 2h, and then reduces it in a significant manner, while MIA PaCa-2 and WI-38 cells did not show marked growth alterations.</td>
<td>Hep-2, Caco-2, SW620, WI-38, MIA PaCa-2</td>
<td>[1]</td>
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<td></td>
<td>Capable of altering the release of cytokines by NK and NK-like cells in response to tumour cells, significantly inhibiting the release of IL-1beta, TNF-alpha, but not of IL-2.</td>
<td>[26]</td>
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<td></td>
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<td>Apoptosis can be detected in cells exposed to sevoflurane</td>
<td>[1]</td>
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<td>Sevoflurane does not induce cytotoxicity in either PC12 cells or primary cortical neurons.</td>
<td>PC12</td>
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*(continued on next page)*
Table 3 (continued)

<table>
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<tr>
<th>Anesthetics</th>
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<tbody>
<tr>
<td>Intravenous</td>
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<tr>
<td>Propofol</td>
<td>Clinically relevant concentrations of propofol inhibit the invasion of human cancer cells: in particular, it prevents pulmonary metastasis of cancer cells by inhibiting invasion activity rather than by inhibiting growth. Propofol-based conjugates (propofol-DHA, propofol-EPA) may be useful for the treatment of breast cancer inhibiting cell adhesion and migration, and inducing apoptosis. The activation of GABA-A receptor by propofol increases the migration of MDA-MB-468 cells. Propofol does not affect the production of nitric oxide or TNF-alpha.</td>
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<td></td>
<td>Hep-2, Caco-2, W620, WI-38, MIA Paca-2</td>
<td>MDA-MB-468</td>
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<td></td>
<td></td>
<td>SH-SY5Y</td>
<td>[39]</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Inhibits the carbachol evoked release without affecting the associated increase in [Ca2+]i, suggesting that etomidate may exert additional effects at either the muscarinic receptor or the secretory machinery in SH-SY5Y human neuroblastoma cells. Etomidate seems not to affect the number of migrating cells.</td>
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<td></td>
<td></td>
<td>MDA-MB-468</td>
<td>[37]</td>
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<tr>
<td>Ketamine</td>
<td>Reduces the activity of NK cells and increases lung tumour retention and lung metastases more than 2.5 fold (effect markedly reduced when pre-treated with [β,adrenergic antagonist — nadodol — or chronic small doses of an immunostimulator is executed). Clinically achievable concentrations of ketamine may suppress some inflammatory responses of both astrocytes and microglia cells treated with LPS: it inhibits LPS-induced PGE2 production in astrocytes and reduces LPS-stimulated production of TNF-alpha in astrocytes, microglia and in glial cells. Ketamine in subnarcotic doses exerts a selective effect on tumour cells. It may have a valuable effect on amelioration of early apoptosis in astrocytoma cells.</td>
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<td>[4,14]</td>
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<td>[38,46]</td>
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<td>[38]</td>
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<td></td>
<td></td>
<td></td>
<td>[47,48]</td>
</tr>
<tr>
<td>Thiopental</td>
<td>In concentrations used during routine anaesthesia, it inhibits tumour-cell killing in a dose-related manner. Thiopental reduces NK activity significantly and increases MADB106 lung tumour retention or lung metastases: effect absent during excision of 3LL tumour, and aggravated by the presence of hypothermia during thiopental-based anaesthesia. Thiopental inhibits both the production of TNF-alpha and NF-kB activation induced by LPS in human glioma cells A-172. In SH-SY5Y cells, thiopental inhibits both K+ - and carbachol-evoked release, causes noncompetitive inhibition of K+ -stimulated Ca2+ influx, inhibits carbachol-stimulated increased intracellular Ca2+ concentrations in the presence and absence of extracellular Ca2+, and has no effect on carbachol-stimulated inositol (1,4,5)-triphosphate formation.</td>
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<td></td>
<td></td>
<td>A-172</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SH-SY5Y</td>
<td>[56]</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>N2O alone or in combination with methionine or methotrexate might be of value for cancer treatment, thanks to synergistic effect on depletion of functional folate, reducing cellular proliferation that significantly affects leukaemic growth. During excision of the 3LL tumour in rats, the use of N2O has no effect on NK cells activity, avoiding postsurgical growth acceleration of metastases.</td>
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effects of this drug on the inflammatory responses of native glial cells highlighting how propofol does not affect the production of nitric oxide or tumour necrosis factor-alpha (TNF-alpha), which play key roles in acute and chronic neurodegenerative processes [34]. Nevertheless, during an open cholecystectomy, a total intravenous anaesthesia using propofol and remifentanil seems to suppress the inflammatory response caused by surgery to a greater extent than a balanced inhalation technique using isoflurane: the plasma levels of TNF-alpha, interleukin IL-6 and interleukin IL-10 – measured at the end of anaesthesia and surgery – are significantly lower in the propofol/remifentanil group than in the group treated with isoflurane [26]. Finally, propofol presents a high potential as an efficient antioxidant in clinical anaesthesia: the administration of this agent prevents oxidative stress, NF-kB activation and inducible nitric oxide synthase (iNOS) overexpression in liver rats receiving halothane [9]. Therefore, the propofol treatment might block the production of noxious mediators involved in the development of halothane-induced injury [9].

**Etomidate** is a short acting intravenous anaesthetic agent used for the induction of general anaesthesia and for sedation in short procedures. The effects of this intravenous anaesthetic induction agent on K+ and carbachol evoked [3H]noradrenaline ([3H]NA) release and [Ca2+]i have been examined by Sikand et al. in their study in vitro in SH-SYSY human neuroblastoma cells [35]. In particular, experimental results have demonstrated how it inhibits the carbachol evoked release while significantly decreasing the associated increase in [Ca2+]i, suggesting that etomidate may exert Q4 additional effects at either the muscarinic receptor or the secretory machinery in these cells [35]. The effects of

### Table 3 (continued)

<table>
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<tbody>
<tr>
<td>Nitrous oxide seems to suppress carbachol-stimulated increases in cytosolic free calcium.</td>
<td>SK-N-SH</td>
<td>[70]</td>
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<tr>
<td>N2O has no effect on TNF-alpha induced E-selectin expression while it decreases TNF-alpha-induced transcriptional activity of NF-kB, highlighting a protective effect of anaesthetic on TNF-alpha-induced endothelial cell damage.</td>
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**Opioids**

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<tr>
<th>Anesthetics</th>
<th>Effects</th>
<th>Cell Line</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Remifentanil</td>
<td>It has no significant effect on neutrophil respiratory burst even in higher concentrations.</td>
<td></td>
<td>[88]</td>
</tr>
<tr>
<td>Morphine</td>
<td>Kuraishi, during his study in mice and using B16-BL6 melanoma cells, showed that administration of morphine suppresses tumour growth and metastases. In MCF-7, MDA-MB231 and HT-29 cells it has been suggested that morphine, alone or in combination with naxalone, may reduce the growth of certain tumours, apparently in part through activation of p53 phosphorylation.</td>
<td>B16-BL6</td>
<td>[102]</td>
</tr>
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<td></td>
<td>Morphine also shows higher cytotoxic activity against three human tumour cell lines: lung carcinoma A549, mammary gland carcinoma MCF7, promyelocytic leukemia HL-60 highlighting how it might provide a new strategy for the treatment and prevention of cancer.</td>
<td>MCF7, MDA-MB231, HT-29</td>
<td>[106]</td>
</tr>
<tr>
<td>NMBDs</td>
<td>Atracurium and cisatracurium, but not mivacurium, inhibit proliferation of human cell lines.</td>
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<td>[118]</td>
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</table>

**Local Anaesthetics**

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Effects</th>
<th>Cell Line</th>
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<tbody>
<tr>
<td>Lidocaine</td>
<td>At the level of tissue concentration under topical or local administration, lidocaine has a direct inhibitory effect on the activity of epidermal growth factor receptor (EGFR), which is a potential target for antiproliferation in cancer cells.</td>
<td>CAL27, HT1080, HOS, RPMI-7951</td>
<td>[129]</td>
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<td></td>
<td>Might be an ideal infiltration anaesthetic for surgical cancer operations.</td>
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<td>[130]</td>
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<tr>
<td>Ropivocaine</td>
<td>Unlike the reported inhibiting effects of local anaesthetics on purified protein kinase C isoforms, no such modulation is found in intact neuroblastoma cells for ropivocaine, lidocaine and bupivacaine.</td>
<td>SK-N-MC</td>
<td>[131]</td>
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<td></td>
<td>It shows little effect on nitrite production (160% of control values) and only at the highest concentration (3.3 mM, corresponding to 890 microg/mL or 0.089% w/v).</td>
<td>C6</td>
<td>[133]</td>
</tr>
<tr>
<td>Procaine</td>
<td>It has growth-inhibitory effects in MCF-7 breast cancer cells, causing mitotic arrest.</td>
<td>MCF-7</td>
<td>[134]</td>
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</table>
single doses of etomidate on adrenocortical function, instead, have been investigated by Absalom et al., in a randomised controlled clinical trial demonstrating how, in the critically ill, single doses of this anaesthetic agent may interfere with cortisol synthesis for at least 24 h [36]. In fact, the use of intravenous anaesthetic, etomidate, for prolonged sedation has been associated with low levels of plasma cortisol and increased mortality; therefore, as etomidate inhibits adrenal steroidogenesis, it is suggested that, when used, treating selected patients with corticosteroids should be considered [37]. In recent years, instead, Garib et al. have investigated, in vitro, the direct influence of etomidate on migration of breast carcinoma cells MDA-MB-468 [33]. While both treatment with propofol and treatment with lidocaine produce an increase of the percentage of migrating cells, as well as the velocity, etomidate does not seem to affect the number of migrating cells [33]. In other words, it does not support cancer progression by suppressing the activity of immune cells.

**Ketamine** is a general dissociative anaesthetic whose effects on cancer have been well investigated. The effects of anaesthesia, with this anaesthetic agent, on lung tumour progression have been well studied. The effects of anaesthetics, except propofol, reduces the activity of NK cell [48]. The results show how ketamine, similarly to other analyzed anaesthetics, except propofol, reduces the activity of circulating NK cells and increases lung tumour retention and lung metastases more than 2.5-fold in all experiments. This effect is markedly reduced when pre-treatment with β-adrenergic antagonist (nadodol) or chronic small doses of an immunostimulator (polyriboinosinic:polyribocytidylic acid) is executed [4]. These results confirm research previously performed by Katzav et al., who found that the use of ketamine during excision of Lewis lung carcinoma (3LL) tumour produces an NK cell activity decrease while, moreover, was reversed following treatment with polyinosinic-polycytidylic acid (poly I:C), an NK cell potentiator [10]. Nevertheless, despite these findings, the use of low-dose ketamine (0.5 mg/kg) — especially in women — was suggested as being beneficial for postoperative pain management after oral maxillofacial surgery, reducing the risk of cancer metastasis caused by suppressing natural killer (NK) cell activity [38]. The effects of this drug on inflammatory responses have also been analyzed: while several studies show how ketamine presents anti-inflammatory action in various immune cells such as macrophage and peripheral leucocytes — stimulated with LPS in vitro and in vivo [39—41], Shibakawa et al., have demonstrated that clinically achievable concentrations of ketamine may suppress some of the inflammatory responses of both astrocytes and microglia cells treated with LPS without causing significant changes in nitric oxide release.

In particular, this anaesthetic agent inhibits LPS-induced prostaglandin E2 (PGE2) production in astrocytes, and reduces LPS-stimulated production of TNF-alpha in astrocytes, microglia and in glial cells [34,42]. Other authors, instead, have investigated the influence of ketamine on hydration processes of tumoural and normal glanular cells, and on the binding of labelled ouabain with tissues in order to reveal changes in the number of active Na–K-ATPase molecules on the cell membrane [43,44]. They have demonstrated, in vitro, how hydration of tumoural and normal cells diminished in 1-h incubation in a solution comparable to anaesthesics, and sub-anaesthetic, concentrations of ketamine, proving that the content of water in the tumoural cells increases and that ketamine in sub-narcotic doses exerts a selective effect on tumoural cells [43,44]. In tumour-bearing mice, the xylazine plus ketamine (XY/Ke) anaesthesia reduces tumour uptake ratios through inhibition of insulin release in mice kept fasting 4 h [45]. In astroglioma cells, ketamine reduces cell shrinkage and increases granularity during the early period, and ameliorates cell swelling during the late reperfusion period, suggesting that it may have a valuable effect on amelioration of early and late apoptosis in astrocytoma cells, even though the exact mechanism remains to be verified [46].

**Sodium thiopental**, better known as thiopental, is a barbiturate anaesthetic agent. Several reports have demonstrated that thiopental inhibits immune responses [47—49]. Duncan et al., showed how thiopental, in concentrations used during routine anaesthesia, inhibits tumour-cell killing in a dose-related manner [50]. In particular, analyzing, in vitro, — by incubating 51Cr-labelled YAA-1 tumour cells obtained from the peritoneal cavities of syngeneic A/JAX white mice, with immune leucocytes from the peritoneal cavities of allogeneic C57/black mice — the effects of this drug on the ability of leucocytes to kill tumour cells, the authors observed how inhibition of cytoxicity ranged from 8.6% at 2.8 × 10−2 m thiopental to 38.1% at 8.5 × 10−2 m thiopental [50]. Similarly, in 1983, Lovett et al. highlighted how a single dose of thiopental (37–42 mg/kg) — sufficient to achieve anaesthesia induction in mice — increased the growth rate of a 3-methylcholanthrene-induced syngeneic murine fibrosarcoma in C57Bl/6 mice with significant alterations in cell-mediated immunity [48]. In accordance with these results, Melamed et al. confirmed how thiopental, similar to other anaesthetic agents, significantly reduces group NK activity and increases MABd106 lung tumour retention or lung metastases [4]. On the one hand, this effect is absent during excision of the 3LL tumour [10], but on the other it can be further aggravated by the presence of hypothermia during thiopental-based anaesthesia. While normalthermic anaesthesia reduces natural killer cell activity to 39±6.2% of control levels, hypothermia reduces it to 15±6.6%, increasing tumour retention to 250% of control levels, and the number of metastases from 1.1±0.4 to 4.7±1.2, placing patients with metastasizing tumours or dormant viral infections at greater risk for complications [51]. The inhibition effect of thiopental, however, also regards tumour necrosis factor-alpha and nuclear factor kappa B. Thiopental, in fact, inhibits both the production of TNF-alpha and NF-kB activation induced by LPS in human glioma cells A-172 [52]; inhibition of NF-kB which, as Loop et al. have demonstrated, is due to the suppression of IkB kinase activity and depends, at least in part, on the barbiturate molecule. In particular, inhibition of NF-kB binding activity by thiopental is not due to GABA receptor stimulation and does not involve direct targeting of activated NF-kB [53]. The results, rather, indicate that thiopental suppresses the NF-kB activating signalling cascade by altering IkB kinase activity, and that the thio-group at the C2 position within the barbiturate molecule plays a key role in mediating this effect [53]. The effects of this intravenous anaesthetic on...
Drugs of anaesthesia and cancer

Potassium K⁺ and carbachol-evoked [3H]noradrenaline release from a human neuroblastoma cell line, SH-SY5Y, have also been investigated: thiopental inhibits both K⁺ and carbachol-evoked release with IC50 values respectively, of 116 ± 15 μM and 169 ± 39 μM; it causes noncompetitive inhibition of K⁺-stimulated Ca²⁺ influx, with IC50 values of 127 ± 7 μM and 121 ± 10 μM; inhibits carbachol-stimulated increased intracellular Ca²⁺ concentrations in the presence and absence of extracellular Ca²⁺, and has no effect on carbachol-stimulated inositol (1,4,5)-triphosphate formation [54].

"Nitrous oxide"

Nitrous oxide (N₂O) is a weak anaesthetic agent and for this reason it is usually not used alone in general anaesthesia, but in combination with more powerful volatile anaesthetic drugs, such as sevoflurane, desflurane, isoflurane or halothane. Its effects on cancer were, and are, subject of numerous studies. Similarly to many other inhalation anaesthetics, also N₂O was suspected of inducing tumours or congenital anomalies in chronically exposed anaesthetic staff. At the end of the 1970s, Coate et al. investigated the effects of prolonged exposure to low-concentration combinations of halothane and nitrous oxide on tumour incidence, especially with regard to the reticuloendothelial system, in rats [55]. The results did not lend support to the hypothesis that these anaesthetic agents, in low concentrations, are responsible for the reportedly higher than average incidence of reticuloendothelial malignancies in operating room personnel [55]. Successively, the study of Kano et al. showed how N₂O alone, or in combination with methionine or methotrexate, might be of value for cancer treatment, thanks to synergistic effects on depletion of functional folate that these drugs have demonstrated [56]. Nitrous oxide, in fact, inactivates the vitamin B12-dependent enzyme methionine synthetase with subsequent impairment of folate metabolism and a reduction of cellular proliferation which, increased by mean cycloleucine, significantly affects leukemic growth [57–59]. Moreover, Katzav et al. showed how the use of N₂O — during excision of Lewis lung carcinoma (3LL) tumour in rats — has no effect on NK cell activity, avoiding, hence, the acceleration of postsurgical growth of metastases [10]. Similarly, Griffith et al. found that exposure to clinically used concentrations of halothane and nitrous oxide does not interfere with the natural killer lymphocyte response in patients with benign and malignant breast diseases [60]. A few years later, however, Ermans' clinical observations in patients treated for breast carcinoma or childhood cancer showed how the use of this anaesthetic, shortly before or during methotrexate administration — used in several chemotherapeutic protocols for the treatment of malignancies — should be avoided as it increases cytotoxic effects of methotrexate on proliferating cells with unexpected myelosuppression and mucosal damage [61]. The same authors suggested how combining the anticolchobalamin activity of N₂O with an anti-folate seems to be a promising chemotherapeutic approach with significant anti-leukemic potential [62]. For example, the reduction of leukemic proliferation by N₂O retards leukemic infiltration of the bone marrow compartment [63]. However, the findings of a randomized controlled clinical trial demonstrated that the administration of nitrous oxide to cancer-bearing patients, but not to those undergoing orthopaedic surgery, produces major changes in amino acid metabolism, and consideration should be given to the avoidance of exposure of cancer patients to nitrous oxide [64]. While the administration of nitrous oxide (60–150 min) to patients undergoing orthopaedic procedures did not affect blood L-methionine, in patients requiring resection of tumours, blood L-methionine concentration was significantly lower and the blood amino acid pattern was significantly affected after the administration of N₂O (120–310 min), compared with values after the induction of anaesthesia and before surgery [64]. The effect of different insufflations of gases, nitrous oxide included, on the implantation of a tumour cell suspension, following laparoscopic surgery, in an established small animal model suggests how the development of metastases in port sites after laparoscopy may be influenced, in part, by the choice of insufflation gas used to create the pneumoperitoneum: while helium is associated with reduced rate of metastases, no significant differences exist between air, carbon dioxide (CO₂), and N₂O [65–67]. Also, the effects of this anaesthetic agent on Ca²⁺ mobilization and membrane potential in the human neuroblastoma cell line, SK-N-SH, have been widely analyzed. In particular, nitrous oxide seems to suppress carbachol-stimulated increases in cytosolic free calcium ([Ca²⁺]i) — that plays fundamental roles in the initiation and regulation of many neuronal processes — by enhancing Na⁺/Ca²⁺ exchange activity [68]. Recently, finally, the impact of different anaesthetics — such as nitrous oxide — on TNF-alpha-induced endothelial cell adhesion molecule expression has been investigated. In particular, the findings suggest that N₂O, similarly to other analyzed agents, has no effect on TNF-alpha induced E-selectin expression, while there is decreased TNF-alpha-induced transcriptionsal activity of NF-kB, highlighting a protective effect of anaesthetic on TNF-alpha-induced endothelial cell damage [69].

"Opioids"

Opioids represent an important cornerstone in treating various types of pain, at all stages of cancer. The relationships between postoperative pain and metastasis — already widely demonstrated in rats — determine that pain management is a critical factor in preventing surgery-induced decreases in host resistance against metastasis, and moreover, becomes a priority in postoperative care [70]. In addition to their therapeutic efficacy, opioids can however produce several well-known adverse events, and, as recently reported, can interfere with immune responses [71]. An adequate knowledge of their effects with regard to cancer, hence, becomes important in order to avoid metastatic diffusion following surgery.

Fentanyl is an opioid anaesthetic agent with an analgesic potency about 80 times that of morphine. Similarly to some lesser degree morphines, it seems to have potential benefits in the treatment and development of bone cancer pain. In a murine model of bone cancer pain, repeated administration of equianalgesic doses of fentanyl (0.16 mg/kg.s.c. once a day) and morphine (20 mg/kg.s.c. once a day) — initiated at day 1 (prophylactic treatment) or at day 7 (curative treatment) after tumour cell inoculation in the
femoral cavity — determines a consistent decrease of bone pain symptoms and tumour growth-induced bone destruction, suggesting how treatments based on these anaesthetic agents show clear antinoceptive properties, as well as reductions in cancer cell-induced bone lesions [72,73]. Shavit et al. investigated the effects of different doses of fentanyl, administered at different time points relative to tumour inoculation, on natural killer cell cytotoxicity (NKCC) and on experimental tumour metastasis, demonstrating how, when used with intermediate doses, fentanyl suppresses NKCC and increases MADB106 lung tumour retention in a correlated manner, increasing the risk of tumour metastasis [74]. Moreover, also large-dose fentanyl administration is more effective in suppression of immunity function than small-doses, as shown by Li et al., analyzing the effects of different doses of this anaesthetic on T-lymphocyte subpopulations and natural killer cells during esophageal cancer surgery under general anaesthesia [75]. Nevertheless, the two types of anaesthesia (with small-dose or large-dose fentanyl) show impressive differences in the rate of recovery of NKCC suppression. On the second postoperative day, NKCC returned to control values in patients treated with small-dose fentanyl administration, whereas NKCC remains significantly suppressed after large-dose fentanyl administration, indicating how the latter approach causes prolonged suppression of NK cell function, and might have a long-term impact on the overall outcome, especially in cancer patients [76,77]. In general, hence, similarly to many other opioids employed in clinical practice, fentanyl does not prevent immunosuppression induced by surgery [71,77,78]. The effects of this anaesthetic agent on [3H] noradrenaline in SH-SY5Y human neuroblastoma cells have also been widely investigated, demonstrating how fentanyl produces a significant, concentration-dependent inhibition of [3H] noradrenaline release [79].

Remifentanil, an ultra short acting opioid, is recommended as an ideal analgesic agent during neurosurgical procedures. It allows perfect titration of the analgesic effects to varying noxious stimulation intensities, along with rapid recovery and early assessment of postoperative neurological function [80,81]. While most studies in literature have widely investigated the effects of this agent on extubation time, recovery and cerebral hemodynamics during procedures, such as non-emergency intracranial surgery or craniotomy for brain tumour resection [82–84], little is still known about the effects of remifentanil on cancer. Nevertheless, the few studies on this argument show how, used in combination with propofol in a total intravenous anaesthesia, remifentanil seems to suppress the inflammatory response caused by surgery to a greater extent than isoflurane used with a balanced inhalation technique [26]. Also, the effects on cellular immune response, a key element for perioperative tumour surveillance, have been investigated, demonstrating how in ASA I–II patients undergoing simple abdominal hysterectomy, remifentanil-based anaesthesia, in combination with adequate analgesia, reduces the counts of natural killer cells that are involved in tumour surveillance and destruction, and determines an increase of neutrophils [85]. Nevertheless, in their study executed in vitro, Jaeger et al. have found that this anaesthetic agent has no significant effect on neutrophil respiratory burst, even in concentrations higher than those encountered during in vivo conditions [86].

Sufentanil is a synthetic opioid analgesic agent, approximately 5–10 times more potent than fentanyl. It is used in operations and critical care sites, where pain relief is required for a short period of time. Moreover, as demonstrated by De Leon-Casasola and Lema [87], sufentanil seems more effective than morphine when administered intraspinally in opioid-tolerant patients. Results suggest that sufentanil should be considered an effective alternative therapy for postoperative pain control in chronic opioid users, using high doses of oral opioids before surgical intervention [87]. The effects of this drug on cancer have been poorly treated in literature. Most studies carried out regard the use of sufentanil in cancer pain management or surgery and were directed to evaluating incidence on time to extubation [83], neurological recovery time [88], intracranial pressure [89], and cost issues [90]. However, the effects of this anaesthetic agent on plasma levels of TNF-alpha, IL-6 and interleukin 8 (IL-8) were examined by El Azab et al., in their analysis on patients undergoing cardiac surgery with cardiopulmonary bypass [91]. In particular, they have demonstrated that while total intravenous anaesthesia with propofol and minimal dose sufentanil, or with a moderate dose of midazolam-sufentanil, affects the pro-inflammatory cytokine response to surgical stimulation before starting cardiopulmonary bypass, it does not modify the pro-inflammatory cytokine response to ischemia–reperfusion or extracorporeal circulation [91], confirming that total intravenous anaesthesia (TIVA) with propofol, sufentanil and atracurium does not seem to have a significant effect on IL-1beta, IL-4, IL-6, TNF-alpha and interferon-gamma (IFN-gamma) release in forty adult patients, ASA I-II, undergoing elective laparoscopic or open cholecystectomy [92].

Morphine, worldwide, is given by several different routes, such as, oral, rectal, subcutaneous, intravenous, epidural or intrathecal, for the relief of cancer related pain [93–97]. The effects of this drug on tumour growth and metastasis have been investigated. Simon and Arbo demonstrated that in rats, the use of morphine produces an increase in metastatic growth [98]. On the contrary, Yeager and Colacchio demonstrated in vivo, that injections of morphine may decrease the growth of tumour cells that gain access to the circulation during a surgical procedure [99]. Similarly, Kuraishi, during his study in mice, and using B16-BL6 melanoma cells, showed that administration of morphine suppresses tumour growth and metastasis [100]. These results were also confirmed by Sasamura et al. in [101]. Sacerdote et al. have demonstrated that morphine, when administered in analgesic doses after surgery in cancer patients, does not affect NK cell activity, which, instead, is significantly enhanced by tramadol administration [102]. In particular, they suggest that tramadol should be used in place of morphine for the treatment of postoperative pain. The inhibitory effect of morphine on experimental lung metastasis and invasion of colon 26-L5 cells, instead, has been investigated by Harimaya et al. demonstrating that this analgesic drug inhibited the adhesive and invasive properties of tumour cells by different inhibitory mechanisms involving the mediation of an opioid receptor [103]. In MCF-7, MDA-MB231 and HT-29 cells it has

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been suggested that morphine, alone or in combination with naxolone, may reduce the growth of certain tumours, possibly in part through activation of p53 phosphorylation [104]. Morphine also shows higher cytotoxic activity against three human tumour cell lines: lung carcinoma A549, mammary gland carcinoma MCF7, and promyelocytic leukaemia HL-60, highlighting how it might provide a new strategy for the treatment and prevention of cancer [105,106]. Nevertheless, in recent years it has been shown that long-term dose-dependent morphine treatment promotes tumour growth, and a DNA vaccine may be a useful approach in treating severe immunosuppressive reaction and preventing tumorigenesis after long-term morphine treatment [107]. Moreover, in a murine model of bone cancer, sustained morphine treatment increases pain, osteolysis, bone loss, and spontaneous fracture, as well as markers of neuronal damage in DRG cells and expression of pro-inflammatory cytokines [108]. Finally, the effects of morphine and its metabolites, such as morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) on immune function in advanced cancer patients, have been analyzed by Hashiguchi et al. [109], demonstrating that part of humoral and cellular immunity is modulated by morphine-derived metabolites at the early phase of morphine therapy, in patients with advanced cancer who required morphine for pain relief [109].

**Alfentanil**, a fentanyl derivative, is a potent analgesic characterized by a quick onset time, short duration of action, low toxicity and short elimination time. Mainly used intraoperatively, it is also adopted postoperatively for pain relief: used intravenously after abdominal operations, it is intraoperatively, it is also adopted postoperatively for pain relief. Aside from its analgesic effect, alfentanil also has antiemetic and anti-secretory properties [110]. Little is known about alfentanil in relation to cancer. The effect of this drug on cancer has been poorly investigated in literature. **Oxycodone** is a semi-synthetic opioid agonist used in controlling cancer pain [111]. In particular, the clinical efficacy of CR oxycodone in cancer-pain control appears at least the same as morphine, with a similar safety profile [112]. **Hydromorphone** is a semi-synthetic derivative of morphine, and is more potent, more soluble and has a comparable side-effect profile [113]. Nowadays, it is often used in the management of cancer-related pain. There is a lack of information about alfentanil, hydromorphone or oxycodone in relation to cancer development.

**Tramadol** is a centrally acting analgesic drug which, often used for treating moderate to severe pain, appears to be a good choice for the treatment of pain in patients where immunosuppression is particularly contraindicated [114]. In particular, when administered after surgery in cancer patients, tramadol shows analgesic activity comparable to that of morphine, but induces an improvement in postoperative immunosuppression, suggesting how it may be preferred for the treatment of postoperative pain with these patients [102]. Moreover, the administration of this opioid, before and after laparatomy, seems to prevent surgery-induced NK activity suppression blocking the enhancement of lung metastasis [115].

**Neuromuscular blocking drugs**

Neuromuscular blocking drugs (NMBDs) are given as part of general anaesthesia. Although NMBDs provide no anaesthesia or analgesia, they eliminate spontaneous breathing and promote mechanical ventilation. The effects of these drugs on cancer have been poorly investigated: the few existing studies have principally analyzed the influence of some of these agents on the proliferation of normal human cells and their pharmacokinetics, and neuromuscular effects in patients with liver disease [116,117]. In particular, in their study executed in vitro on hepatoma HepG2 cells and human umbilical vein endothelial cells, Amann et al., have demonstrated that atracurium and cis-tracurium inhibit proliferation of human cell lines, but not mivacurium, and that this effect is alleviated by glutathione and N-acetylcysteine, as well as by the carbonyl esterase [116].

**Regional anaesthesia and cancer**

In vitro data and in vivo animal studies suggest that three factors associated with cancer surgery impair cellular immunity, increasing the risk of cancer recurrence [118,119]: stress response to tissue injury, general anaesthesia, and opioid analgesia. Regional anaesthesia, instead, seems a valuable solution capable of decreasing this risk, reducing the neuroendocrine stress response to surgical tissue injury, eliminating or decreasing the need for general anaesthesia, and minimizing opioid requirement [118]. Results also confirmed the association between regional anaesthetic techniques at primary cancer surgery and reduced incidence of metastatic disease [120]. Similarly, Groetelaers and colleagues, in their follow-up study after five years, show how axillary recurrence is significantly reduced (only 0.8% encountered) after sentinel lymph node biopsy under local anaesthesia for breast cancer [121]. Kumar et al. have investigated the use of spinal anaesthesia with a micro-catheter as a primary method of anaesthesia for colorectal cancer surgery, and other major abdominal surgery in high-risk patients for whom general anaesthesia would be associated with higher morbidity and mortality [122]. However regional anaesthesia based on para-vertebral blocks (PVB) can be successfully performed for breast cancer surgery in the majority of patients, significantly reducing nausea, vomiting, pain and other side-effects [123]. Hashimoto and colleagues demonstrated that epidural anaesthesia blocks the effect of stress induced by major surgery (such as gastrectomy) on fluctuation of peripheral lymphocyte subpopulations, which may be associated with immunity suppression [124].

**Lidocaine** is a common, local anaesthetic and antiarrhythmic drug that can also be used for controlling pain in cancer patients. In agreement with what was reported recently by Sharma et al., a single IV infusion of lidocaine provided a significantly greater magnitude and duration of pain relief in opioid-refractory patients with cancer pain [125]. Similarly, intravenous lidocaine may be an effective alternative to opioids in the treatment of refractory malignant pain in the paediatric patient with terminal cancer [126]. At the level of tissue concentration under topical or local administration, lidocaine has a direct inhibitory effect on the activity of epidermal growth factor receptor (EGFR), which is a potential target for anti-proliferation in cancer cells [127]. In particular, in a human tongue cancer cell line, CAL27, concentrations of lidocaine...
400 μM and 4000 μM show an antiproliferative effect – respectively, with and without cytotoxicity – suggesting that the inhibition of epidermal growth factor (EGF)-stimulated EGFR activity is one of the basic mechanisms of the antiproliferative effect of this drug. Moreover, lidocaine, at concentrations used in surgical operations (5–20 mM), seems able to effectively inhibit the invasive ability of human cancer (HT1080, HOS, and RPMI-7951) cells modulating ecotdomain shedding of heparin-binding epidermal growth factor-like growth factor (HB-EGF), demonstrating that it might be an ideal infiltration anaesthetic for surgical cancer operations [128].

Ropivacaine is a local anaesthetic drug which, developed after bupivacaine, is usually adopted for infiltration, nerve block, epidural and intrathecal anaesthesia in adults, and children over 12 years. The effects of this anaesthetic agent on protein kinase C function in vitro were examined in both mouse Neuro-Za neuroblastoma cells and muscarine M1-receptor mediated phosphoinositide breakdown in human SK-N-MC neuroblastoma cells [129]. In particular, the study demonstrated that unlike the reported inhibiting effects of local anaesthetics on purified protein kinase C isoforms, no such modulation is found in intact neuroblastoma cells for ropivacaine, lidocaine and bupivacaine [129].

The effect of this local anaesthetic agent on the energy metabolism of Ehrlich ascites tumour cells has been investigated by Di Padova et al., suggesting how it impairs energy metabolism of Ehrlich ascites tumour cells by affecting primarily, mitochondrial metabolism [130]. Ropivacaine, at all concentrations tested, stimulated aerobic lactate production, and this increase, in addition to the inhibition of respiration, was also due to an activation of mitochondrial ATPase [130]. Also, the effects of ropivacaine on the expression of calcium-independent nitric oxide synthase (NOS2) have been examined in immunostimulated rat C6 glioma cells [131]. Unlike bupivacaine and high dose lidocaine, it shows little effect on nitrite production (160% of control values) and only at the highest concentration (3.3 mM, corresponding to 890 μg/mL or 0.089% w/v) [131].

Procaine is a local anaesthetic drug, first synthesized in 1899, used less frequently today. As demonstrated by Villar-Garea and colleagues in their 2003 study, procaine is a DNA-demethylating agent that has growth-inhibitory effects in MCF-7 breast cancer cells, causing mitotic arrest [132]. The synthesis of procaine, together with that of cisplatin, represents the basis of Cis-diaminechloro[2-(diethylamino) ethyl 4-aminobenzoate, N(4)-chloride platinum (II) monohydrochloride monohydrate (DPR). This new platinum triamine complex seems to be an antitumour agent able to trigger apoptosis, endowed with a peculiar mechanism of action and a special selective activity against two tumours, namely neuroblastoma and small cell lung cancer (SCLC), which are still characterized by a low incidence of long-term survivors [133]. Moreover, when simultaneously administered with standard anticancer agents DPR, it appears to promote cytikilling [134].

Discussion and conclusion

Anaesthetical drugs, acting on intracellular pathways, are able to trigger biomolecular cascades involved in different physiological and pathophysiological cellular functions, such as proliferation, angiogenesis and apoptosis [1,2,4]. Therefore, drugs of anaesthesia, probably interacting with functional modules such as molecular complexes, signalling networks, and whole organelles, often regulate cellular processes that may result in genetic dysfunction. Finally, genetic disorders, with different gene expression, may explain a possible role of anaesthetic drugs in cancers, but the findings present in the current literature are very confusing, and it is difficult to draw any firm conclusions. In fact, there seems to be a potential, strong correlation between volatile anaesthetic drugs and cell survival. In particular, inhaled anaesthetics such as isoflurane and halothane, modify tumour cell growth in a time dependent manner [1], whereas Huafeng Wei et al. suggest that isoflurane and sevoflurane differentially affect cell survival [22]. Moreover, isoflurane but not sevoflurane, induces cytotoxicity with different mechanisms. Finally, there is weak evidence that volatile anaesthetic agents mediate cellular and systemic homeostatic responses to reduced O2 availability in mammals, including erythropoiesis, angiogenesis, and glycolysis [1]. Some authors suggest a possible role of barbiturates in apoptosis and therefore in tumour development and progression [53,135].

The role of anaesthesia and immune response is also significant. There is evidence that an anaesthetic regime is able to induce an immunosuppressive state in humans, resulting in an ineffective immune response, and therefore may contribute to genetic disorders, thereby playing a role in tumour genesis. It has been observed that propofol, an intravenous agent, inhibits the invasion activity of different cancer cells [2,4]. Moreover, this anaesthetic agent seems to have a beneficial effect on antitumour immunity, at least in mice [30]. Similar to volatile agents, intravenous drugs seem to have some apoptotic functions. Finally, the role of anaesthetic drugs as a molecular delivery system, such as that proposed by Siddiqui et al., is a very interesting, but still weak, proposal. These authors described the synthesis, purification, characterization and evaluation of two novel anticancer conjugates, propofol-docosahexaenoate (propofol-DHA) and propofol-eicosapentaenoate (propofol-EPA), showing how these propofol-based conjugates may be useful for the treatment of breast cancer [31].

There are many interpretations for these surprisingly varied available data. The first is that the most of these results are related to studies performed in vitro: therefore, at present, they should be viewed as hypothesis generation. These anaesthetic mechanisms in modulating tumour behaviour should be tested systematically in animal models and also in clinical studies, where different anaesthesia techniques are performed and many anaesthetic drugs co-administered [136]. In fact, the relative weakness of the findings specifically addressing these issues is mainly due to the lack of clinical studies. Moreover, in experiments, some authors use anaesthetic drugs in a wide range of clinically relevant doses. On other hand, the argument cannot be simply ignored, as the care staff is today still unable to understand the weight of the problem and give answers to the patients’ and families’ questions. There is the suspicion that several anaesthetics are used for cancer resection, even if clinical effects on the behaviour of cancer cells are unclear, despite having been reported that invasion, or metastasis of cancer cells easily occurs during surgical...
procedures, and that, in general, there is evidence supporting the fact that, by virtue of some still unknown mechanisms, anaesthesia regime may influence physiological cellular and/or molecular process involved in tumour development, finally raising the question if, at all, it should be considered socially acceptable and safe. This kind of knowledge could therefore be a basic valuable support to improve anaesthesia performance and patient safety.

Cell Lines cited in the text

51Cr-labelled YAAC-1
A-172
A-549
B104
B16
BL6
C6
Caco-2
CAL27
Hep-2
Hep3B
HepG2
HL-60
HOS
HT1080
HT-29
MAD8100
MAD8106
MCF7
MDA-MB231
MDA-MB-468
MIA-Paca-2
PC12
RPMI-7951
SH-SY5Y
SK-N-MC
SK-N-SH
SW620
WI-38

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Drugs of anaesthesia and cancer


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List of abbreviations used in the text

[Ca++]: Cytosolic free calcium;
3LL: Lewis lung carcinoma;
Abeta: Amyloid beta protein;
APP: Amyloid precursor protein;
Bax: BCL2-associated X protein;
Bcl2: B-cell CLL/lymphoma 2;
Ca2+: Calcium ion with a 2+ charge;
CGRP: Calcitonin gene-related peptide;
CO2: Carbon dioxide;
DNA: Deoxyribonucleic acid;
EAAT3: Excitatory amino acid transporter type 3;
ER: Neuronal endoplasmic reticulum;
GABA: Gamma-aminobutyric acid;
GABA-A: Gamma-aminobutyric acid type A;
HIF-1: Hypoxia inducible factor 1;
IC50: 50% Inhibitory concentration;
IFN-gamma: Interferon-gamma;
IL-1 beta: Interleukin-1 beta;
IL-10: Interleukin-10;
IL-1beta: Interleukin 1beta;
IL-2: Interleukin-2;
IL-4: Interleukin 4;
IL-6: Interleukin-6;
IL-8: Interleukin 8;
inOS: Inducible Nitric Oxide Synthase;
Ins(1,4,5)P3: Inositol(1,4,5)Triphosphate;
LPS: Lipopolysaccharide;
LD: Lipodolsaccharide;
mRNA: Messenger RNA;
N2O: Nitrous Oxide;
NF-kB: Nuclear Factor kappa B;
NK: Natural Killer;
NKCC: Natural Killer Cell Cytotoxicity;
NMBDs: Neuromuscular Blocking Drugs;
O2: Oxygen;
PGE2: Prostaglandin E2;
PMCA: Ca(2+)-ATPase;
poly I:C: Polyinosinic–Polycytidylic Acid;
propofol-DHA: Propofol-Docosahexaenoate;
propofol-EPA: Propofol-eicosapentaenoate;
Rho A: Ras homolog gene family, member A;
RNA: Ribonucleic Acid;
Th1/Th2: T helper 1/T helper 2;
TIVA: Total Intravenous Anaesthesia;
TNF: Tumour Necrosis Factor;
TNF-alpha: Tumour Necrosis Factor-Alpha;
Xy/Ke: Xylazine plus Ketamine

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