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# Anesthesia in cancer patients: can anesthetic techniques and agents influence the outcome? A narrative review

## *Anestesia no paciente oncológico: as técnicas e agentes anestésicos podem influenciar o desfecho destes pacientes? Uma revisão narrativa*

**Felipe Rangel[1], Claudia Marquez Simões[2], José Otávio Costa Auler Jr[3]**

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**ABSTRACT:** *Introduction*: Anesthesia in cancer patients represents a challenge in many ways: complex patients with various comorbidities and often undergoing adjuvant treatments. Surgical treatment is the first-line treatment in most cancer cases, and anesthesia is an essential step to make this treatment possible. The use of different anesthetic agents and techniques today is one of the potential factors that may influence cancer outcome. We reviewed some of the new concepts that have emerged in the literature regarding perioperative anesthetic care and the evolution of this population. *Methods*: A narrative and exploratory bibliographic study. A search was performed on the Medline and Scielo databases using the terms (((anesthesia) OR (anesthesia)) AND (cancer)) until November 2019, and 44 studies were included. Results: These studies discuss the specific role of various anesthetic agents, especially intravenous, inhalational and opioid hypnotic agents, and address the possible differences between anesthetic techniques. We included not only the anesthetic agents themselves but also the role of other agents frequently used in the perioperative period. Conclusions: Regional anesthesia techniques still need to be studied further but they may bring benefits to this population by assisting in perioperative pain control, reducing opioid consumption and inflammation triggered by the stress response. Not enough evidence exists to modify the agents and techniques used in anesthesia, but there are some indications of potential benefits for intravenous anesthesia, opioid-sparing multimodal analgesia techniques, and even for the use of some agents such as lidocaine and propofol. Little clinical evidence supports the use of fully opioid-free anesthesia aimed to reduce recurrence and optimize the outcome of the cancer patient, but this subject is being widely studied and soon there will be more news and evidence that may redirect perioperative anesthetic management.

**Keywords**: Anesthesia; Neoplasms; Recurrence.

**RESUMO**: *Introdução*: A anestesia no paciente oncológico representa um desafio sob vários aspectos: pacientes complexos, com diversas comorbidades e, muitas vezes, submetidos a tratamentos adjuvantes. O tratamento cirúrgico é o tratamento de primeira linha em grande parte dos casos oncológicos e a anestesia é uma etapa essencial para viabilizar este tratamento. O uso de diferentes agentes e técnicas anestésicas hoje é visto como um dos potenciais fatores que podem vir a influenciar o desfecho oncológico. Revisamos alguns dos novos conceitos que têm surgido na literatura, referentes aos cuidados anestésicos perioperatórios e a evolução desta população. *Métodos*: Estudo bibliográfico narrativo e exploratório. Realizada pesquisa nos bancos de dados Medline e SciELO, utilizando os termos (((anesthesia) OR (anaesthesia)) AND (cancer)) até novembro de 2019 e 44 estudos foram utilizados. *Resultados*: Os estudos discutem o papel específico de diversos agentes anestésicos, principalmente agentes hipnóticos endovenosos, inalatórios e opioides, além de abordarem as possíveis diferenças entre as técnicas anestésicas. Além dos agentes anestésicos propriamente ditos, o papel de outros agentes frequentemente utilizados no período perioperatório foram incluídos. *Conclusões*: Técnicas de anestesia regional ainda necessitam ser mais estudadas, mas podem trazer benefícios para esta população auxiliando no controle álgico perioperatório, reduzindo o consumo de opioides e a inflamação desencadeada pela resposta ao estresse. Ainda não há evidências suficientes para modificação dos agentes e técnicas utilizadas na anestesia, mas existem alguns potenciais benefícios sinalizados para o uso de anestesia venosa, técnicas de analgesia multimodal poupadora de opioides e, até mesmo, o uso de certos agentes como a lidocaína e o propofol. Poucas evidências clínicas respaldam o uso de anestesia totalmente livre de opioides com o objetivo de reduzir a recorrência tumoral e otimizar o desfecho do paciente oncológico, mas o assunto está sendo amplamente pesquisado e brevemente haverá mais novidades e evidências que poderão redirecionar a conduta anestésica perioperatória.

**Descritores:** Anestesia; Neoplasias; Recidiva.

1. Pós-graduando. Instituto do Câncer do Estado de São Paulo (ICESP). ORCID: https://orcid.org/0000-0002-1131-7535. E-mail: felipe.rangel@hc.fm.usp.br.
2. Supervisora. Instituto do Câncer do Estado de São Paulo (ICESP). ORCID: https://orcid.org/0000-0002-4306-5168. E-mail: claudia.simoes@hc.fm.usp.br.
3. Prof. Titular da Disciplina de Anestesiologia da Faculdade de Medicina FMUSP da Universidade de São Paulo. Instituto do Câncer do Estado de São Paulo (ICESP). ORCID: https://orcid.org/0000-0002-3919-1743. E-mail: jose.otavio@fm.usp.br.
**Mailing address:** Claudia Marquez Simões. Av. Dr. Arnaldo, 251 - 13º andar. CEP: 01246-000 - São Paulo, SP, BR.

## INTRODUCTION

Anesthesia in cancer patients presents a challenge in several aspects: they are complex patients, with several frequent comorbidities, submitted to adjuvant treatments often before the indication for surgical treatment[1]. At the same time, anesthesiologists may still have to deal with the treatment of severe and difficult-to-control chronic pain in some cases. Therefore, nowadays the question is how anesthesia, its techniques and agents may influence the evolution of these patients and even facilitate or protect them against any tumor recurrences. Surgical treatment will be first-line treatment in most cancer cases, and anesthesia is an essential step to enable this treatment[2]. The use of different anesthetic agents and techniques today is seen as one of the potential factors that may influence cancer outcome[3]. With this in mind, we aimed to review some of the new concepts that have emerged in the literature regarding perioperative anesthetic care and the evolution of this population.

## METHODOLOGY

This is a narrative and exploratory bibliographical study. A search of the Medline and SciELO databases using the terms (((anesthesia) OR (anaesthesia)) AND (cancer)) was performed until November 15, 2019, considering original studies. In total, 757 articles were identified from the defined search criteria. Of these, 2 reviewers initially selected the relevant articles, and the main articles were used.

### Perioperative period and the risk of metastasis

Although surgery is an indication for curative intent, the perioperative period is at high risk for tumor cell dissemination. Tumor cells may spread and, when finding a favorable environment, they may implant and allow late tumor recurrence. The immune system will play an essential role in controlling these cells that may fall into the circulation and both the surgical stress and the anesthesia itself may have a direct influence on the action of the immune system[3]. Therefore, it has been postulated that perhaps better anesthetic control during the perioperative period may have an impact on long-term tumor recurrence[2]. In fact, both different anesthetic techniques[4,5] and anesthetic agents[6–8] may lead to greater or lesser immunosuppression, besides having other actions that favor or inhibit tumor spread. Accordingly, they become part of the broad spectrum of factors that may influence the evolution of the cancer patient.

### Anesthetic Agents

Some *in vitro* and animal studies have suggested that some anesthetic agents may influence tumor cell survival through various mechanisms such as interference with intracellular signaling mechanism to apoptosis, cytoskeleton formation and modulation of neuroendocrine response to trauma, among others. From this initial evidence, some clinical studies were conducted to confirm such hypotheses. Yet, there are still controversial results in the literature.

#### Propofol

Propofol is a hypnotic agent, widely used for both induction and maintenance of anesthesia. Propofol also has anti-inflammatory and antioxidant effects, which may play a protective role against perioperative immune suppression. Propofol leads to downregulation of oncogenes and regulates tumor suppressor genes in different cells[9].

Nuclear factor kappa B (NF-κB) is a protein complex that controls DNA transcription, cytokine production and cell survival, and its poor regulation is associated with cancer. Propofol induces inhibition of tumor cell growth and apoptosis via inhibition of NF-κB nuclear activity. This hypnotic agent also restricts cell migration and invasion, having a potential protective effect against tumor spread, thereby reducing tumor recurrence following surgical manipulation. Other authors have shown that propofol also acts on hypoxia-inducible factor 1-alpha, an essential factor in regulating metastatic tumor growth and proliferation[10]. Another function shown in the laboratory is the activation of caspases, leading to the activation of apoptosis, i.e., the activation of intrinsic and extrinsic pathways of cell death.

Metamieloproteinases (MMPs) are capable of degrading the extracellular matrix and are responsible for a series of cellular behaviors such as proliferation, adhesion and angiogenesis. Propofol inhibits MMP-2 and MMP-9, preventing proliferation, invasion and angiogenesis of esophageal, lung and colorectal cancer cells[9].

Existing evidence points to potential advantages of using propofol in cancer patients. Nevertheless, further clinical studies are required to understand the behavior of this hypnotic agent at the doses and durations used in the clinical setting, which may vary and have different results from those observed *in vitro* and in animals.

#### Inhalational Anesthetics

Inhalational anesthetics compromise numerous immune functions including neutrophils, macrophages, dendritic cells, T cells and natural killer (NK) cells. These agents also upregulate the hypoxia-inducible factor and have antiapoptotic properties, which may promote tumor cell proliferation[11].

A clinical study comparing the use of inhalational agents with propofol in a retrospective analysis of elective surgery showed a higher risk rate for patients receiving

anesthesia with halogenated agents[12].

In a large retrospective study of more than 5000 breast cancer patients, the authors did not find any association between the anesthetic technique used and long-term prognosis and tumor recurrence[13].

In renal carcinoma cells, isoflurane caused an upregulation of hypoxia-inducible factors 1-alpha and 2-alpha, leading to an increased expression of endothelial growth factor[14]. Moreover, the cells exposed to isoflurane also showed higher capacity of migration. Such findings may reveal that isoflurane, a very frequently used agent, is capable of having a pro-tumor effect.

On the other hand, other studies show a potential protective effect of halogenated agents, including isoflurane itself. A study of hepatic carcinoma cells indicated that isoflurane has inhibitory effects mediated by the regulation of the NF-κB15 signaling pathway[15]. In addition, isoflurane is able to inhibit apoptotic resistance via the activation of caspase-3 and -8. Therefore, isoflurane may be, among halogenates, an agent with potential beneficial effects for the clinical treatment of patients with hepatic carcinoma.

In this respect, it has been observed that there is little data from clinical studies, and most of it is retrospective. The main studies showing and postulating the mechanisms of action of halogenated agents in tumor cells are *in vitro* or experimental. Therefore, further clinical evidence is still needed, and the results of some prospective ongoing clinical studies may provide more accurate data on the possible benefits or risks of using halogenated agents. There is still insufficient evidence to refute the use of inhalational agents[16], but much remains to be clarified regarding their effects and indications for the cancer population.

### Lidocaine

Lidocaine is an extremely versatile agent that has been widely used as a cornerstone of multimodal analgesia. Lidocaine has anti-inflammatory effects that help inhibit the development of tumor cells, besides having a potential protective effect[17]. Lidocaine has also been shown to increase NK cell activity, enhancing the body's immune protective effect against tumor cells[18].

Several mechanisms have been proposed for the potential protective effect of lidocaine against tumor cells, such as: inhibition of epidermal growth factor receptor, inhibition of cell division in a dose-dependent manner, increase in caspase-3 activity, cytotoxicity and DNA demethylation of some tumor cells, among other effects[19].

Lidocaine has even been studied for joint use with cisplatin, for its antitumor effects, and may constitute a new therapeutic option for some types of tumors, such as hepatocellular carcinoma[20].

### Anti-inflammatory drugs

Proliferation of cancer cells is closely linked to the prevention of inflammation. Thus, anti-inflammatory drugs have been studied for their potential protective effect on tumor recurrence. When used in patients who underwent resection of breast tumors, ketorolac and diclofenac led to longer postoperative disease-free time and longer survival[21].

Other non-steroidal anti-inflammatory drugs have also shown a protective role against the progression of some tumors, as demonstrated by the use of low doses of acetyl salicylic acid for HER-2-positive breast tumors[22]. The use of low doses of aspirin was also protective for other types of tumors, such as gastric[23] and colorectal tumors[24].

### Opioids

Opioids are key agents for perioperative analgesic therapy. However, the use of these drugs in cancer patients has been widely questioned. Opioids have a dose-dependent immunosuppressive effect that can be extremely deleterious in this population. Thus, this is the rationale for the use of opioid-sparing or opioid-free techniques for cancer patients. Recently, the role of immunosuppressants has also been debated, as the opioid action is much more complex and may have an immunostimulatory or double effect[25].

The administration of fast-acting opioids at low doses appears to have a positive impact on the immune system. However, comparatively, chronic and high-dose use has a negative impact.

On the one hand, opioids can prevent inflammation and inhibit tumor growth, but on the other hand, at high doses and with prolonged use, they can aggravate the inflammatory reaction, have an immunosuppressive effect and induce and increase infection rate. It is noteworthy, however, that much is still under investigation concerning the use of opioids in the cancer population. Nonetheless, we can state that pain control is the key to success, and if there are no more options for pain control, opioids are still the main therapeutic option in perioperative analgesia. Additionally, pain control may have the same importance as seeking to avoid or reduce opioid consumption, as pain also leads to a deleterious immunosuppressive effect in cancer patients[26,27].

## Other agents

### Beta blockers

Studies in animal models suggest that the surgical stress associated with the spread of neoplastic cells favors the retention of these cells in certain metastatic target organs. Preclinical studies suggest that beta-blocking agents may have a protective effect against tumor progression.

Beta-adrenergic receptors are present in tumor and immune cells[28] and signaling through these receptors accelerates the spread of neoplastic cells[29]. Some *in vivo*

studies have shown that treatment with beta-blockers prevents metastases by inhibiting tumor cell invasion[30], tumor-associated inflammation and neoangiogenesis, thereby limiting tumor spread[31].

However, some meta-analysis studies conducted recently show divergent results. Yap et al.[32] reviewed retrospective studies investigating the association of beta-blocker use with tumor recurrence, disease-free survival and overall survival, and no beneficial effects of beta-blockers on tumor recurrence were found. Furthermore, benefits regarding the disease-free period and overall survival are equally divergent among the studies included in this meta-analysis. Similarly, another meta-analysis reported no association between beta-blockers and tumor progression[33].

Hence, given the controversial findings, further clinical trials should be performed to better evaluate the influence of beta blockers on cancer progression.

**Dexamethasone**

The use of dexamethasone in the perioperative period is interesting as it helps in the prophylaxis of postoperative nausea and vomiting and has an adjuvant effect in the treatment of postoperative pain, both intravenously and perineurally, prolonging the effect of local anesthetics[34].

It is well known that glucocorticoids induce generalized immunosuppression, which could have a deleterious effect at a time when a large spread of neoplastic cells occurs, such as during oncologic surgeries. Dexamethasone, in particular, can significantly suppress lymphocyte production and inhibit the NK cell function thus promoting resistance to tumor cell apoptosis[35].

Nevertheless, a recent cohort study evaluated patients undergoing mastectomy to assess the use of dexamethasone for tumor recurrence, finding no increase in tumor recurrence among patients using this drug[36].

Therefore, further studies should be conducted to assess whether the use of dexamethasone may increase the risk of tumor recurrence among other subtypes of cancer.

**Anesthetic technique**

The relationship between anesthetic technique and tumor recurrence has been extensively studied. The theoretical benefits of regional anesthesia are based on the modulation of the neuroendocrine response and reduced opioid consumption, thereby preserving the immunological function of patients, besides the direct effects of local anesthetics on tumor cells[37,38].

However, studies have shown conflicting results regarding disease-free time and patient survival. Biki et al.[39] carried out a retrospective analysis comparing patients undergoing radical prostatectomy under general anesthesia versus combined anesthesia, epidural and general, and found that the group undergoing combined anesthesia had a lower risk of biochemical recurrence (PSA). In another study, Koumpan et al.[40] compared patients with noninvasive bladder cancer who underwent transurethral resection of the bladder under spinal anesthesia versus general anesthesia and observed that patients in the spinal anesthesia group had a lower incidence of tumor recurrence.

Nonetheless, a meta-analysis of 28 studies and more than 67,000 patients found no relationship between regional anesthesia and reduced tumor recurrence or patient survival[41]. A prospective, randomized, triple-blind pilot study evaluated patients undergoing mastectomy comparing general anesthesia combined with paravertebral versus only general anesthesia, and to date there has been no difference in tumor recurrence between groups[42].

## CONCLUSIONS

Metabolic and neuroendocrine response plays an essential role during the perioperative period and in the success of surgical treatment in cancer patients. Anesthesia has the potential to reduce this response, inhibit inflammation, control pain and, by several other molecular mechanisms, positively or negatively influence cancer progression.

Regional anesthesia techniques still need to be studied further, but they may bring benefits to this population by assisting in perioperative pain control, reducing opioid consumption and the inflammation triggered by the metabolic neuroendocrine response to stress.

Currently, there is still not enough evidence for the complete change of anesthetic agents and techniques for cancer patients, but there is indication of potential benefits to use venous anesthesia, opioid-sparing multimodal analgesia techniques and even some specific agents such as lidocaine and propofol. To date, little clinical evidence supports the use of fully opioid-free anesthesia in order to reduce tumor recurrence and optimize the outcome of the cancer patient[43,44]. Nevertheless, the subject is widely investigated currently, and soon there will be more news and evidence that may redirect perioperative anesthetic management.

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