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NARRATIVE REVIEW

Anesthetic Immunomodulation and the Tumor Recurrence: A Narrative Literature Review

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Abstract

Introduction: Surgical interventions and the anesthesia chosen for the procedure induce immunosuppression in the perioperative period, triggering the release of pro-inflammatory cytokines, favoring tumor growth and recurrence. However, it must be clarified what actually influences immunomodulation: the surgical technique, the anesthetic used, the type of tumor or a combination of all of them.

Methods: This is a narrative review of literature with a bibliographic search in MEDLINE (PubMed) and BVS databases. Papers in English and Spanish that presented combinations of the following descriptors were included: "Immunomodulation"; "Opioids"; "Anesthesia"; "Immune System"; "Anesthetics" and "Neoplasm Recurrence".

Results: The database search resulted in seventy-four articles. The main findings are listed in Table 1.

Conclusions: Anesthetic immunomodulation still has unclear findings regarding its positive or negative influence on tumor recurrence and progression, and more research is needed related to the immunological mechanisms of anesthetics, especially intravenous and opioids.

Keywords

Immunomodulation, Anesthesia, Neoplasm recurrence

Introduction

Both the surgery and anaesthetic technique can exert immunomodulatory effects, and, therefore, they may contribute to the progression of metastases and tumor recurrence. The hypothalamus-pituitary-adrenal (HPA) axis is responsible for regulating the immune system and stress response and during the perioperative period, the activation of the HPA axis induces immunosuppression [1]. The release of pro-inflammatory cytokines (e.g. Tumor Necrosis Factor (TNF) alpha, interleukins (IL) 10 and 4) in this process is related to tumor growth, development of metastases and angiogenesis [2-4]. Nevertheless it remains to be clarified the real impact of anesthetic modality on tumor recurrence and progression. Several trials have demonstrated deleterious responses - development of metastases and tumor recurrence - while others showed a protective effect - decreased chances of tumor growth - according to these variables. The literature suggests that volatile anesthetics have greater negative immunomodulatory effects, as well as opioids. On the other hand, regional anesthesia-analgesia has a protective effect in some *in vitro* assays.

From 2008 to 2018, the incidence of cancer grew by about 25% worldwide and about two thirds of these patients have undergone some type of surgical procedure requiring anesthesia [5]. Hence, studying and discussing the effects of anesthesia and its relationship with tumor recurrence is of great relevance to the scientific context of world health.

Materials and Methods

This is a narrative review of the literature with

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a bibliographic survey carried out from the analysis of articles published in MEDLINE (PubMed) and BVS databases. It was included works in English and Spanish from 2016 on, that presented combinations of the following descriptors: “Immunomodulation”; “Opioids”; “Anesthesia”; "Immune System"; “Anesthetics”; “Neoplasm Recurrence"; "Onco-anesthesia"; "Opioid free anesthesia". Eight-five articles were found, being thirty-six selected. It was included in the review the studies cited in the selected articles that showed concordance with the theme and the inclusion criteria: study that analyzed whether there was tumor recurrence, analysis of the immune response related with several anesthetic agents, sample quality and year of the studies publication (Figure 1).

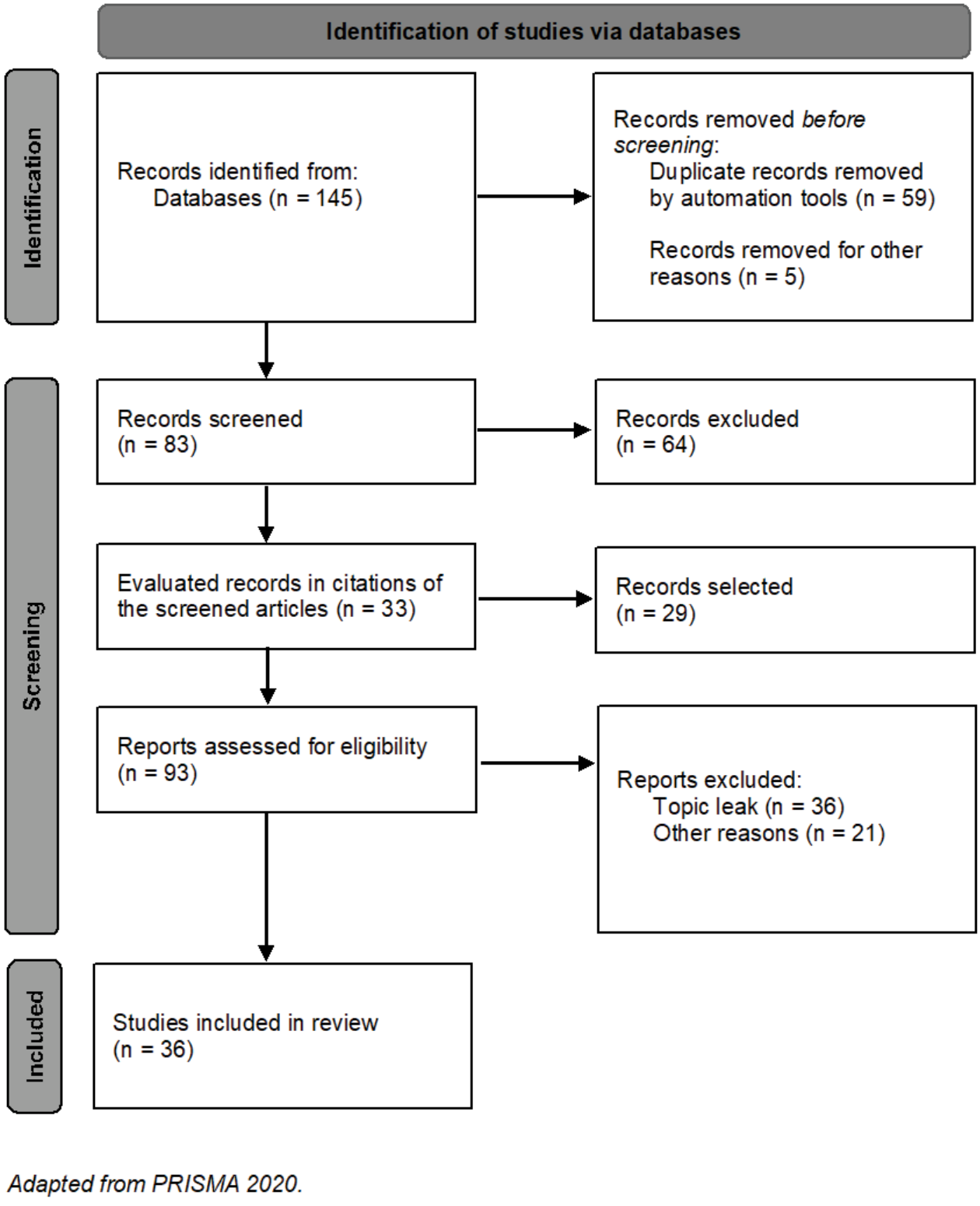

Figure 1: Identification of studies via databases.

Results

Eighty-five articles were retrieved from the databases. Following, the exclusion and inclusion criteria - time of publication of the study, type of study and quality of data provided - were applied. After careful analysis, thirty-six studies were selected and nineteen of them are listed in Table 1 [6-24] based on the main findings.

Table 1: Summary of the main findings of the selected articles.

Gao M, Sun J, Jin W, Qian Y [6]	Th1 and Th2 cells, levels of INF-γ, IL-2, IL-4 and T-bet and GATA3 activities increased significantly after incubation with PMA and ionomycin. However, the number of Th_1, Th_1/Th_2 cells, INF-γ and INF-γ/IL-4 levels and activities/levels of T-bet and GATA3 were decreased after incubation with PMA and ionomycin in the presence of morphine. Naloxone can abolish the suppressive effect of morphine in the differentiation of Th cells. Morphine has a negative effect in the Th cell balance induced by PMA and ionomycin, the mechanism is related to T-bet and GATA3.
Shakhar G, Ben-Eliyahu S [7]	Minimizing postoperative immunosuppression seems feasible, it can limit tumor recurrence and should be considered when planning oncologic surgeries. In the short term, doctors could try to avoid immunosuppressive anesthetic approaches, inadvertent hypothermia, excessive blood transfusions and untreated postoperative pain. When possible, minimally invasive surgery should be considered. Long term clinical trials should evaluate prophylactic measures, including perioperative immunostimulation and various antagonists of cytokines and hormones specified herein.
Page G, Ben-Eliyahu S, Yirmiya R, Liebeskind J [8]	The results support the hypothesis that activity suppression of NK cells mediates increasing surgically induced metastatic colonization. Besides, an analgesic dose of morphine blocked the surgery-induced increase in metastasis without affect metastasis in unoperated animals. These findings suggest that postoperative pain is a critical factor in promoting metastatic spread. If a similar relationship between pain and metastasis occurs in humans, pain control must be considered a vital component of postoperative care.
Forget P, Collet V, Lavand'homme P, De Kock M [9]	Surgery, analgesics and coexisting conditions influence cellular immunity significantly. The importance of these changes varies with time. Fentanyl had a worse influence than clonidine and ketamine, but it seemed equally protective against the development of metastases.
Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S [10]	This study in a mouse model of lung metastasis demonstrates that some anesthetics increase the tumor metastasis susceptibility, apparently by suppressing the natural killer cell activity. Ketamine was more deleterious and its effects were prevented by peripheral blockade of the beta-adrenoceptors combined with low levels of immunostimulation.
Kim R [11]	Local anesthetics such as lidocaine increase the activity of NK cells. Anesthetics such as propofol and locoregional anesthesia, which decrease neuroendocrine responses induced by surgery through the HPA axis and the suppression of the SNS, can cause less immunosuppression and recurrence of certain types of cancer compared to volatile anesthetics and opioids.
De Kock M, Loix S, Lavand'homme P [12]	Ketamine appears as a unique "homeostatic regulator" of acute inflammatory reaction and stress induced immune disorders. This is of some interest at a time when short- and long-term deleterious consequences of inappropriate inflammatory disorders reactions are increasingly reported. However, large scale studies showing improvement in patient outcome, are needed before definitively asserting the clinical reality of this positive effect.
Chang Y, Chen TL, Sheu JR, Chen RM [13]	This study shows that a clinically relevant concentration of ketamine [100 microM] may suppress macrophage function of phagocytosis, its oxidative capacity and inflammatory cytokine production, possibly by reducing the mitochondrial membrane potential rather than direct cell toxicity.
Blandino-Rosano M, Barbaresso R, Jimenez-Palomares M, Bozadjieva N, Werneck-de-Castro JP [14]	Rapamycin treatment decreases CPE expression and Insulin secretion in mice and human pancreatic islets. We suggest an important role of mTORC1 in β-cells and we have identified the downstream pathways that lead to β-cell mass, the function and processing of insulin.
Shapiro J, Jersky J, Katzav S, Feldman M, Segal S [15]	Current experiences indicate that the anesthetic drugs used during surgical excision of two tumors from different mice can cause a significant increase in metastatic propagation and progression. These drugs also caused the dissemination of metastases to organs in which metastases were not found. The possibility of similar phenomena of metastatic acceleration occurring in other mice tumor systems or in other mammals, or with other anesthetics, requires further study.
Kim R, Emi M, Tanabe K [16]	In fact, not just the modulation of cell death induced by anticancer drugs, but also the activation of antitumor immune responses using molecularly targeted drugs such as antibodies and small molecules, may provide a remarkable increase of chemotherapeutic effects in cancer therapy. More studies are needed on cellular and molecular mechanisms to contribute to anti-tumor immune responses.

Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, et al. [17]	Adding spinal block to general anesthesia with halothane markedly attenuates the promotion of metastases by surgery.
Melamed R, Rosenne E, Shakhar K, Schwartz Y, Abudarham N, et al. [18]	The findings point to possible prophylactic measures in cancer patients undergoing surgery and suggest a role for MP-NK cells in resistance to metastasis of apparently insensitive tumors.
Shakhar G, Abudarham N, Melamed R, Schwartz Y, Rosenne E, et al. [19]	MP-NK cells are unique in their ability to kill apparently immunoresistant tumor. Low doses of synthetic ds-RNA and potentially Th_1 cytokines may expand this MP-NK population and protect it from immunosuppression. The news of such a prophylactic approach is to direct the immediate postoperative period, which is characterized by high vulnerability to residual disease, and to protect critical anti-metastatic immunity against postoperative suppression. The use of such an intervention potentially innocuous in cancer patients who are preparing for surgery might reduce metastatic recurrence.
Le Cras AE, Galley HF, Webster NR [20]	Spinal anesthesia may result in less immunosuppression after surgery. The study found that the proportion of T help cells 1 for T help cells 2 was higher in patients undergoing prostate surgery under spinal anesthesia instead of general anesthesia. Th_1 cells promote protective immune responses that may result in fewer postoperative infections.
Angele MK, Faist E [21]	Although significant advances have been made, it is important to better define the pathophysiology and identify the mechanisms responsible for cell mediated immunity depression using experimental animal models. The effective treatments regimen may be developed only when injury models begin to consider them as factors.
Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G [22]	The results indicate that the stress-induced suppression of NKA is enough to cause tumor intensified development. Under certain stressful conditions, the suppression of NKA is the primary mediator increasing the tumor, while in other conditions, additional factors play a significant role. The clinical circumstances in which surgical stress can induce increased metastatic growth are discussed.
Staudt LM [23]	Various oncogenic abnormalities in epithelial cancers, including mutant K-ras, involve non conventional IkappaB kinases to activate NF-kappaB. The inhibition of constitutive NF-kappaB signaling in each of these cancers induces apoptosis, justifying the development of NF-kappaB pathway inhibitors for cancer treatment.
He H, Chen J, Xie WP, Cao S, Hu HY, et al. [24]	The findings provide new insight into the effects of ketamine in cancer treatment; we suggest that ketamine, which has been widely used in cancer surgeries and for pain relief in patients with chronic cancer, may not be the best choice because it may worsen cancer through anti-apoptosis promotion.

Discussion

Recurrence and tumor progression induced by anesthesia

Although surgery is the treatment of choice for most cancers, it is known that its approach has some caveats, both in terms of metastases and neoplastics cell dispersion. Procedure- and anesthetic-induced immunosuppression may contribute for tumor recurrence and progression [7,8]. Recent studies have shown that this effect on immunity is related to the type of drug chosen, the dose and the patient's age [7].

Immunosuppression occurs owing to decreased activity of macrophages, T lymphocytes and Natural Killer (NK) cells, which, in turn, act in defense against infected e tumor cells, due to its cytotoxic activity, detailed later. Because there is a reduction in these cells - mainly NK cells - during the anesthetic induction, before the surgical procedure, the immune response is decreased, which favors the progression of metastases in oncologic patients [7,9,17-19]. The balance between lymphocytes T CD4+, Th_1 and Th_2 is significantly impaired during surgery, affecting the production of cytokines such as interferon γ (IFNγ), which boosts the cytotoxic capacity of defense cells - NK and T - and interleukin 4 (IL4), responsible for antagonizing the IFNγ [20-22].

Another aspect that influences immunosuppression is the endocrine-metabolic response to trauma caused by surgery. This process triggers an inflammatory cascade that results in increased vascular permeability, proliferation, dispersion and tissue adhesion of tumor cells, mainly mediated by the Src tyrosine kinase enzyme [23,25].

NK cells

NK cells are part of the immune system and they are the main cells related to cytotoxic activity in tumor cells, preventing their growth, progression and recurrence [9,15,16]. They are lymphoid cells from innate immunity that do not express antigen-specific receptors, such as T cells or as B cell immunoglobulins. NK cells can change their behavior according to previous exposure to the antigen, through a divergent mechanism from other cells [26]. Apoptosis occurs through the release of granules with perforins and granzymes, which promote lysis of the target cell [27]. It is known that NK cells are reduced in number and metabolic activity in obese patients, a factor that may be related to the increased incidence of malignant neoplasms in this population [28].

A study with rats undergoing laparotomy under general anesthesia demonstrated that intravenous anesthesia with ketamine may significantly reduce

NK cell activity before surgery, however, it increased the activity of these cells in the postoperative period. Another situation observed was the reduction of lung metastases in these animals [9]. In a study by He, et al. ketamine was tested on human breast tissue cancer cells and it was found that in these cells, there was an increase in anti-apoptosis protein levels, a fact that possibly increased the capacity for cell invasion and proliferation [24]. Shapiro, et al. and Melamed, et al. observed that the use of intravenous anesthetics (e.g. ketamine and thiopental) stimulated lung and liver metastases spread in animal models due to decreased NK cell activity.

Although there are many differences in the studied populations (i.e. age, immunosuppression by external factors, anesthetic choice and dose), most studies have shown that NK cells are the main responsible for preventing tumor progression and that anesthetics decrease the activity of these cells, consequently, favoring the recurrence and dissemination of metastases.

Ketamine immunomodulation

Ketamine is able to act on several receptors, such as NMDA (N-methyl-d-aspartate), ion channels, sigma receptors, among others. Therefore, it is a very versatile drug in its applications [12]. Ketamine's immunomodulation capacity is a new attribute that has become the target of scientific research, given the great interest of the authors for its already known analgesia and inflammation reduction properties.

Chang Y, et al. described the ketamine´s ability to suppress the production of pro-inflammatory cytokines. The decrease in tissue production of nitric oxide (NO) is related to the lower macrophage activity, which in turn is linked to lower production of pro-inflammatory cytokines [13]. A 2017 study by Blandino-Rosano, et al. showed the effect on inflammation by ketamine through a mouse assay. According to the study, the acute effect of the drug is pro-inflammatory, however, it chronically has an anti-inflammatory effect, reducing the action of both TNF-alpha and IL-6 [14] He, et al. suggested that ketamine prevented apoptosis of tumor cells responsible for breast cancer through Bcl-2, a family of mammalian genes and the proteins produced by them, capable of regulating the permeability of the mitochondrial outer membrane - which could be both pro- and anti-apoptotics [24].

Studies indicate deleterious effects of ketamine on immune cells, with the reduction of Th_1 and Th_2 cells and the consequent decrease of cytokines responsible for the immune response against pathogens during infection. This effect has also been observed with some opioids (e.g. morphine), which are widely used to control postoperative pain, making it important further investigation on the effects of both drugs to reduce medium and long-term damage to patients [6,20-22].

Influence of opioids on tumor recurrence

A systematic review conducted by Pérez-González, et al. (2017) showed that there is no consensus on the influence of anesthesia-analgesia on tumor recurrence. Some studies have shown that regional anesthesia (RA) provided a protective effect for some types of cancers - especially gastric cancers, prolonging the survival of these patients [29]. Breast cancer, on the other hand, presented, in rare studies, with the use of RA, the opposite outcome, with tumor growth in mice [30].

Sessler, et al. (2019) demonstrated *in vitro* and *in vivo* that intravenous anesthetics, especially propofol, have a protective effect on the immune system, being preferable compared to volatile ones. Therefore, the combination of regional anesthesia and propofol could provide protection against tumor recurrence in oncologic surgeries. However, other studies have not shown the same outcome, hence, there is no superiority between both anesthesia techniques, regarding tumor recurrence [31].

Opioids and onco-anaesthesia

Several factors lead to perioperative immunomodulation, such as surgical stress, surgical duration, extensive manipulation and pain. The use of opioids plays an important role regarding surgical and anaesthetic techniques. The influence of opioids on tumor recurrence and the spread of metastases still lack scientific evidence, since the surgical procedure itself might spread tumor cells during manipulation [30]. Another relevant point is that there are several types of opioids (e.g. morphine, fentanyl, tramadol) and the immunomodulation among them is different.

A limiting factor observed is the lack of prospective studies in humans. The evidence found so far come from *in vitro* and *in vivo* studies and the few studies in humans are retrospective and they have not been conclusive [30-32]. Further studies with proper design are needed to help define the choice of anesthetic techniques [32-34].

At the time of this review, there is no way to define a single cause for tumor recurrence, since several factors are related to it, and therefore, the anesthetic factor should not be implicated in isolation. Likewise, different types of opioid may have different effects on the oncological mechanism. It is known that there is a higher expression of μ opioid receptors in cancer cells, therefore, μ agonist opioids - fentanyl and morphine - May predispose to angiogenesis and tumor growth, by mechanisms that are still poorly understood.

Moreover, many other factors like surgical duration, hypothermia, hypotension, inflammatory response could be related to immunomodulation and consequently could predispose to tumor recurrence.

Thus, multimodal anesthesia could bring great

benefits to patients as it advocates the combination of several drugs with synergistic effect in order to provide adequate analgesia and less adverse effects.

Multimodal anaesthetic techniques provide effective pain control - which is an immunomodulatory factor - and, up to the time of this review, it is the technique of choice for onco-anaesthesia [30,35].

Conclusion

The greatest difficulty found in the compiled studies is the heterogeneity of the clinical conditions studied. Cancer patients have different characteristics, making it difficult to draw conclusions from the observed effects. Another important point is that, although research regarding the immunomodulatory effects of anesthesia is not so recent, the literature lacks studies with long-term results. Besides, those found might be misinterpreted, due to, along with other types of bias, evolution in cancer treatments, which in itself improves prognosis. Thus, further studies are needed to define the role of different types of anesthesia in tumor recurrence and progression, in order to better establish future approaches.

Conflict of Interest Statement

Gabriele Silveira, Isadora Fraga, Larissa Castro, José Lucas Gomes, MD and Marina Delgado, MD, declare that they have no competing interests in conducting this review.

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