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Chapter

Anesthesia Management to Improve Outcomes

Gonzalo Irizaga and Gonzalo Angulo

Abstract

Neoplastic pathology is the second cause of death in developed countries. In our specialty, there is great concern about the implications of the anesthetic technique and the drugs used, present in the perioperative period of the cancer patient; as well as other perioperative factors. Among the latter, we highlight the management of psychological stress, adequate pain control, the type of surgery, avoiding hypothermia, and reducing transfusions of blood products. This concern is based on the fact that despite great advances in both surgical techniques for tumor resection and neoadjuvant and adjuvant polychemotherapy techniques; tumor recurrence rates have not decreased as desired. This suggests that the previously mentioned perioperative factors play an active role in tumor recurrence in cancer patients. Based on current evidence and our experience, we can affirm that the use of anesthetic/analgesic techniques based on the use of propofol, NSAIDs, and regional anesthesia with local anesthetics that achieve a decrease in the perioperative consumption of opiates, especially morphine, can be beneficial to protect the anti-metastatic immune response of the organism in a period of special protumoral susceptibility such as the perioperative period.

Keywords: Anesthesia, surgery, cancer recurrence, bone tumors, osteosarcoma, regional anesthesia

1. Introduction

Neoplastic pathology is the second leading cause of mortality in adults in developed countries. The World Health Organization (WHO) as well as the Pan American Health Organization (PAHO) in their 2017 review, states that in 2015 cancer caused 8.8 million deaths worldwide. They stand out as the cancers with the highest number of deaths; lung cancer, hepatocarcinoma, colorectal cancer, gastric cancer, and breast cancer [1]. In Latin America, according to PAHO statistics, cancer is the second cause of death in the region, it is estimated that 2.8 million people are diagnosed each year and 1.3 million people die from this disease annually [1]. In about 50% of diagnosed cases, there is some degree of metastasis, this being responsible for more than 90% of cancer deaths. Surgical resection is the main treatment for malignant tumors, and in many cases; the only potentially curative treatment. Despite the constant development of new surgical techniques and both chemotherapy and radiotherapy treatments, the incidence of tumor recurrence has changed very little over time. This
suggests that there could be other important factors, some of them apparently linked to the surgical procedure, which may play a fundamental role in the progression of neoplastic pathology and the appearance of metastases. There is a growing interest in understanding these factors and the potential effect that anesthesia and its different techniques may have on them [2, 3].

Anesthetic drugs can induce changes in cell pathophysiology such as cell proliferation, angiogenesis, and apoptosis, and may be determinant in the progression of oncological disease in patients. This is why we are interested in identifying the main perioperative factors that play a role in tumor recurrence in cancer patients who undergo surgery; as well as evaluating which drugs may or may not be beneficial in the perioperative period [3–5].

2. Bone tumors

Bone tumors are characterized by abnormal growth of tissue, which appears and develops into a defined tissue. In the musculoskeletal system, tumors can develop in both bone and soft tissue. Primary tumor lesions at the bone level are relatively infrequent, presenting an incidence of 0.2% of all malignant tumors in the body and preferentially affecting adolescents and young people [6]. Bone tumors can be benign or malignant and within these, primary or metastatic.

The most common bone tumors are bone metastases, multiple myeloma, and primary malignant bone tumors. The most common malignant bone tumor in adults is metastasis from lung, breast, and prostate carcinomas. These appear in advanced stages of the disease and mark a reduction in survival [6, 7]. There are three common primary bone sarcomas, Osteosarcoma, Ewing’s Sarcoma, and Chondrosarcoma.

At the time of diagnosis, 15–20% of patients have metastases, of which 90% are pulmonary. This determines a significant drop in patient survival, which can reach 20–25% at 5 years. Once diagnosed, treatment is classically based on neoadjuvant polychemotherapy, surgery, adjuvant polychemotherapy, and eventually radiotherapy. Survival has increased dramatically thanks to polychemotherapy based on different drugs. Tumor reduction induced by polychemotherapy makes limb preservation possible, using conservative surgery techniques; sometimes complex, which guarantee a satisfactory reception from the oncological point of view. When the surgical margins achieved are not satisfactory, radiotherapy could be considered [8, 9].

2.1 Osteosarcoma

Osteosarcoma is defined according to the WHO as a malignant tumor characterized by the formation of bone or osteoid substance by tumor cells. After myeloma, osteosarcoma is the most common primary bone tumor. It represents about 20% of malignant tumors and about twice as many cases as Ewing’s sarcoma and chondrosarcoma [6]. Its clinical presentation is variable depending on the type, location, and age of the patient. It generally affects more men than women, between the ages of 10 and 25, with a higher peak in the second decade of life. It is very rare under 5 years of age. There is a second peak of incidence in people older than 35 years; almost always related to previous processes such as Paget’s disease, fibrous dysplasia, or irradiation [7].

This malignant neoplasm is characterized by forming bone or osteoid substance directly and encompasses a wide variety of lesions that differ in their clinical and
radiological presentation, microscopic appearance, and evolution. Depending on their location in the bone, 3 groups can be distinguished: superficial osteosarcomas, intracortical osteosarcomas, and intramedullary or central osteosarcomas; the latter being the most frequent. Among intramedullary tumors, various types of high-grade malignancy can be identified: the so-called classic or conventional form, telangiectatic osteosarcoma, and the small cell variant [8]. Although osteosarcoma can affect any bone; it is preferentially located in the metaphyses of long bones. It sits mainly on the knee; distal end of the femur (40%), proximal end of the tibia (15%), or upper end of the femur or humerus (14%), areas that correspond to the bone segments with the greatest growth of the skeleton [8]. (Figures 1–4) shows part of preparation of the bone piece in a knee osteosarcoma resection surgery in a young patient.

2.2 Ewing’s sarcoma

Ewing’s sarcoma is primarily a disease of adolescence, with a peak incidence of about three cases per million in the 15–19 year age group. Although rare, Ewing’s sarcoma is the second most common bone sarcoma affecting children and adolescents. It is more frequent in men; mainly affects Caucasians; and frequently occurs in the spine, pelvis, arm, or leg [7, 8].
Figure 2.
Bone drilling.

Figure 3.
Sterilization with liquid nitrogen.
2.3 Chondrosarcoma

Chondrosarcoma is the most common bone sarcoma in adults. It mainly affects patients older than 50 years. The incidence is 8 per million inhabitants. Chondrosarcomas most commonly arise from the pelvis, upper femur, and shoulder girdle. The prognosis of chondrosarcoma varies depending on the primary location and the extent of spread [7, 8].

3. Antitumor immunity

The development of the primary tumor and its eventual ability to spread to a distance will depend on a balance between the potential for metastatic growth of the tumor and the immunity of antitumor host defense factors. The body’s main anti-metastatic defense mechanism is the immune system, which is evident in the high frequency of malignant tumors that develop in immunosuppressed people or under immunosuppressive treatment [4, 10].

Helper T lymphocytes (Th) are the main intrinsic modulators of the immune system, regulating the two main pathways of specific defense: cellular and humoral, through the secretion of cytokines. The profile of cytokines secreted by Th lymphocytes
polarizes the immune response towards a predominantly cytotoxic or cellular one (Th1) or towards the other end, fundamentally humoral (Th2). These responses are antagonistic. In surgical procedures, the balance is tilted towards increased Th2 production, which is detrimental to cellular immunity and, consequently, the ability of cytotoxic T lymphocytes (CD8+) to fight tumor cells that may have detached from the tumor or that were already present far from the tumor during the surgical procedure [11].

CD8+ T lymphocytes, mononuclear cells, dendritic cells, and especially natural killer (NK) cells are the components of immunity to which anti-metastatic action has been attributed. Cellular immunity at the expense of NK cells plays a fundamental role in tumor recurrence and survival [12]. NK cells are known to be the first line of defense against the development of primary tumors and cells with metastatic spread. They are cells with an immediate response, capable of spontaneously recognizing and destroying tumor cells, identifying the cells as their own or foreign, through the expression of the major histocompatibility complex type 1 (MHC-1). When a cell expresses MHC-1, it inhibits the action of NK cells; and when it is absent, as occurs in tumor cells, they release the content of their granules that destroy the tumor cell membrane [13]. The reduction of its activity can cause an increase in the development of tumors, both primary and facilitate distant dissemination [14]. Patients with low levels of NK cell activity preoperatively have a higher incidence of cancer-associated morbidity and mortality. In favor of the above, a better prognosis has been observed after tumor resection in patients with high levels of NK cell activity at the time of surgery [15]. After surgical damage, an inflammatory reaction occurs at the local level that produces the secretion of proinflammatory cytokines: tumor necrosis factor-alpha (TNF-α), interleukins IL-1b, IL-6, IL-12, IL-15, IL-18, and interferon-gamma (IFN-γ). The primary objective of the inflammatory response that appears after any surgical intervention is to repair and heal damaged tissues. In response to the proinflammatory state, an anti-inflammatory state is then produced in order to restrict inflammation to the injured tissues. Anti-inflammatory mediators are interleukins IL-4, IL-6, IL-10, IL-11, IL-13, and transforming growth factor beta (TGF-β), as well as catecholamines, prostaglandin E2 (PGE2), glucocorticoids, alpha-melanocyte-stimulating hormone (α-MSH), interleukin-1 receptor antagonist (IL-1Ra), and soluble TNF receptors [3].

There is evidence that the inflammatory process is responsible for much of the immunosuppression that appears after surgery and that inflammation itself has a tumorigenic role [16].

Vasodilation that occurs during inflammation is primarily mediated by nitric oxide (NO) and prostaglandins (PGE2, prostacyclin), being a factor that facilitates the supply of soluble mediators and inflammatory cells to the damaged area. These lipid mediators are produced by arachidonic acid through the action of cyclooxygenase (COX) and are considered pro-angiogenic since they serve to heal damaged tissue through the neoformation of vessels, this effect favoring the development of micrometastases [3].

Tumors larger than 2 millimeters (mm) are dependent on the formation of new blood vessels to receive the oxygen supply necessary to continue growing; therefore, for a micrometastasis to develop, an angiogenic process is needed, which will invariably occur when tissue is damaged. It has been seen that overexpression of vascular endothelial growth factor (VEGF) in colorectal cancer is associated with increased invasiveness and metastatic potential of the tumor [17].
4. Perioperative factors that potentiate or inhibit immune responses

During surgical procedures, there are multiple factors related to surgery that determine secondary depression of immunity. Within these, we find psychological stress, tissue damage typical of the surgical act, pain, hypothermia, blood transfusion and factors related to the drugs used that generate alterations in immunity [3-5].

4.1 Non-pharmacological perioperative factors

4.1.1 Perioperative psychological stress

The psychological stress of the patient who is going to undergo surgery can contribute to producing immunological alterations. This happens through sustained activation of the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal axis (HPA). The perioperative activation of the HPA axis will determine the release of adrenocorticotropic hormone (ACTH) and cortisol, which will result in the release of glucocorticoids from the cortex of the adrenal glands with the consequent immunosuppressive effect; as well as an increase in the secretion of plasma catecholamines, adrenaline, and noradrenaline. The latter seem to be the key biomarkers in the relationship between stress and cancer progression [18]. The protumoral effect secondary to the elevation of plasma levels of catecholamines has been attributed to the fact that some tumors express β1 and β2 adrenergic receptors on tumor cells, which favor cell migration, angiogenesis and impair cellular immunity. This cellular immune depression begins preoperatively and can last for several days after surgery [19]. Bartal et al. found that the number of CD8+ T lymphocytes and CD4+ T lymphocytes was lower in patients in the hours prior to surgery compared to patients who were not going to undergo surgical procedures [16].

4.1.2 Surgical act

Surgery is the most effective treatment for cancer, but it is usually associated with systemic release of tumor cells. Tumor manipulation during resection may result in a “spill” of tumor cells into the bloodstream and lymphatic vessels. On the other hand, after surgery, the balance between pro- and antiangiogenic factors is shifted towards angiogenesis to facilitate tissue healing, which may favor tumor recurrence, metastasis formation, and activation of latent micrometastases [5]. The implantation of distant metastases focuses on the so-called “seed and soil” hypothesis; (seed and fertile land) described more than 100 years ago. It tries to explain the non-random location of the metastases of a primary tumor so that only certain tumor cells have the ability to colonize certain organs that have a suitable microenvironment for their growth [20]. It is known that the less aggressive the surgical trauma, the better preservation of the perioperative immune function, and therefore, the greater the trauma, the greater the probability of tumor recurrence; This is why it is proposed in some studies that the reduction of surgical trauma through the laparoscopic technique could reduce the probability of tumor recurrence in cancer patients [21, 22]. As previously mentioned, the surgical act encompasses multiple factors that favor tumor progression and dissemination. Among them, we highlight inadequate pain management, tissue injury related to surgery, hypothermia, and the need for transfusion of blood products.
4.1.3 Pain

Acute pain results in suppression of NK cell activity. It is a powerful stimulant of the HPA axis and its poor perioperative management could be of great importance in favoring tumor recurrence. Optimal pain control can attenuate postoperative immunosuppression and, therefore, tumor recurrence [3, 13, 14, 19, 23]. Postoperative pain in patients undergoing bone tumor resection surgery is significant. Chung et al. [24] examined pain patterns in the postanesthetic recovery unit and found that orthopedic patients had the highest incidence of pain in the outpatient setting. There are many approaches to postoperative pain management, each of which must be tailored to the patient’s pre- and postoperative course. Cancer patients often have pain prior to their surgery and may also be receiving significant amounts of opioids to control it. We must have an accurate idea of our patient’s tolerance and opioid requirements, and we must plan accordingly.

4.1.4 Hypothermia

Hypothermia can also influence the patient’s immune system with the consequent impact on tumor recurrence. Impairs immune functions related to granulocyte chemotaxis and phagocytosis; as well as interfering with the production of antibodies [25]. An inhibition of the oxidative immune response on bacteria and a decrease in the phagocytic capacity of neutrophils and the generation of oxidative reaction intermediates have also been observed, in addition to exacerbating the immunosuppressive effects of surgery. Probably, the immunosuppressive effect of hypothermia is triggered by sympathetic discharge and consequent adrenal release of catecholamines, noradrenaline, and adrenaline, determining suppression of NK cells. Therefore, we believe that temperature monitoring, as well as the adoption of perioperative warming measures, will be extremely beneficial [26].

It has been shown that hypothermia increases the risk of requiring blood transfusions due to bleeding secondary to coagulopathies and platelet dysfunction; this is determinant of immunomodulation [17].

4.1.5 Perioperative transfusion of blood products

Perioperative anemia is present in 25–75% of cancer patients who are going to undergo surgery and is an independent risk factor for morbidity and mortality [27]. Tumors are relatively vascular structures and are therefore prone to bleeding throughout the intraoperative period. Metastases from kidney tumors and thyroid cancers cause significant neovascularization and can bleed dramatically during surgery, much more than other types of bone metastases. Optimizing preoperative hemoglobin values is of vital importance when it comes to reducing the need for transfusion of blood products [28].

Immunosuppression associated with blood transfusion is known in the literature as TRIM (transfusion-associated-immunomodulation) [29]. The effect of transfusion on immunity was suspected due to the better evolution of patients who underwent kidney transplantation and who had been transfused with more than 10 units of blood intraoperatively compared to patients who had not been transfused. In the transfused patients, the viability of the transplant was frankly higher [30]. Blood transfusions are
associated with a reduction in Th cells and NK cells and a reduction in the production of cytokines, including IL-2 and IFN-γ [31]. Amato et al. [32] showed in a meta-analysis that perioperative blood transfusion was an independent risk factor for colorectal cancer recurrence.

4.2 Drugs

Anesthetic drugs can induce changes in cell pathophysiology, such as cell proliferation, angiogenesis, and apoptosis, which can be determinants of the progression of cancer in patients [4]. Anesthesia alters the functions of immune cells, including neutrophils, macrophages, dendritic cells, T lymphocytes, and NK cells [33]. Some of the drugs frequently used in general anesthesia have an inhibitory effect on natural-killer cell-mediated immunity, particularly morphine, ketamine, thiopental, and inhalational anesthetics [24], on the other hand, it would seem that propofol, non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetics have shown promising results (Table 1) [3-5].

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Family</th>
<th>Effects on immunity</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric oxide</td>
<td>Inhalation Anesthetic</td>
<td>• Inhibits the formation of hematopoietic cells that are important in cellular immunity.</td>
<td>Anesthetic induction</td>
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<tr>
<td></td>
<td></td>
<td>• Associated with an acceleration in the development of lung and liver metastases.</td>
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<tr>
<td>Sevoflurane/Isoflurane</td>
<td>Volatile Anesthetics</td>
<td>Immunosuppression:</td>
<td>Anesthetic induction and maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreases the number and function of NK cells, as well as induce lymphocyte apoptosis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Determine an increase in HIF and angiogenesis.</td>
<td></td>
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<tr>
<td>Etomidate</td>
<td>Imidazole</td>
<td>Reduces macrophage function</td>
<td>Anesthetic induction</td>
</tr>
<tr>
<td>Propofol</td>
<td>Alkylphenol</td>
<td>• Promotes the cytotoxicity of NK cells.</td>
<td>Anesthetic induction and maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduces the motility and invasiveness of tumor cells, inducing their apoptosis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• β-adrenergic antagonism. Partial blockade of the HPA axis with the consequent immunoprotective response.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inhibition of COX-2 (antiangiogenic).</td>
<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>Barbiturate</td>
<td>Reduces both the number and activity of NK cells</td>
<td>Anesthetic induction and maintenance</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Phencyclidine</td>
<td>NK cell suppression</td>
<td>Anesthetic induction and maintenance</td>
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DOI: http://dx.doi.org/10.5772/intechopen.106672
### Bone Tumours - A Comprehensive Review of Selected Topics

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Family</th>
<th>Effects on immunity</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam/Diazepam</td>
<td>Benzodiazepines</td>
<td>Inconclusive results</td>
<td>Anesthetic induction and maintenance</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>α2 adrenergic agonist</td>
<td>• In tumors that express α receptors, it can enhance cell growth and proliferation.</td>
<td>Anesthetic induction and maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inhibits the maturation and proliferation of dendritic cells.</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Morphine</td>
<td>Opiates</td>
<td>Morphine has been linked to immunosuppression through:</td>
<td>Analgesia</td>
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<tr>
<td></td>
<td></td>
<td>• Decrease in the number and activity of NK cells.</td>
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<td></td>
<td></td>
<td>• Inhibition in the production of immunostimulatory cytokines such as IFN-γ and IL-2.</td>
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<td></td>
<td></td>
<td>• Less T lymphocyte proliferation and activation.</td>
<td>Promotes angiogenesis by stimulating HIF secretion.</td>
</tr>
<tr>
<td>Fentanyl/Remifentanil</td>
<td></td>
<td>Inconclusive results</td>
<td>Analgesia</td>
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<tr>
<td>Tramadol</td>
<td></td>
<td>Stimulates the activity of NK cells</td>
<td>Analgesia</td>
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<tr>
<td>Ketoprofen/Ketorolac</td>
<td>NSAIDs</td>
<td>COX-2 inhibition</td>
<td>Analgesia</td>
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<td></td>
<td></td>
<td>• Increases the activity of NK cells.</td>
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<td>• Reduces angiogenesis.</td>
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<td>• Increases cell apoptosis.</td>
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<td>COX 2 inhibitors</td>
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<tr>
<td>Lidocaine/Bupivacaine</td>
<td>Local Anesthetics</td>
<td>Increase the activity of NK cells and cytotoxic T lymphocytes.</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Cardioselective β blockers</td>
<td>β-adrenergic blockers</td>
<td>• Block β-receptors of tumor cells.</td>
<td>Arterial Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decrease catecholamine-associated immunosuppression.</td>
<td>Ischemic heart disease</td>
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<td></td>
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<td>• Heart failure</td>
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<td></td>
<td></td>
<td>• Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Statins</td>
<td>Anti-inflammatory, immunomodulatory and anti-angiogenic effect.</td>
<td>Lipid-lowering</td>
</tr>
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<td>Glucocorticoids</td>
<td>Dexamethasone</td>
<td>Inconclusive results</td>
<td>Anti-inflammatory</td>
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<td></td>
<td></td>
<td></td>
<td>Analgesic</td>
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<tr>
<td></td>
<td></td>
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<td>Antiemetic</td>
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</tbody>
</table>

**NK**: natural killer. **HIF**: Hypoxia inducible factor. **HPA**: Hypothalamus pituitary adrenal. **NSAIDs**: Non-Steroidal Anti-Inflammatory Drugs. **COX-2**: Cyclooxygenase 2.

Table 1. Pharmacological implications in immunosurveillance.
4.2.1 Inhaled anesthetics

4.2.1.1 Nitrous oxide

Nitrous oxide interferes with DNA, purine, and thymidylate synthesis, depressing neutrophil chemotaxis. Thus, it inhibits the formation of hematopoietic cells which may be important in tumor surveillance. Additionally, neutrophil function is depressed, and mononuclear cell production reduced. In studies with mice, it has been seen that nitrous oxide is associated with an acceleration in the development of lung and liver metastases, being the most powerful stimulator of liver metastases of the anesthetics studied [34].

4.2.1.2 Volatile agents

In vitro and in vivo studies have shown that there is an association between inhalation anesthesia and increased tumor spread [35–37]. In a recent retrospective study, conducted in 2016 by Wigmore et al. [36] cancer patients were found to have a worse survival outcome if they received inhalation anesthesia. Inhalational anesthetics suppress the immune system by decreasing the function of NK cells, which play an important role in protecting against the proliferation of cancer cells. Inhalational anesthetics induce apoptosis in lymphocytes, reduce NK cell-mediated cytotoxicity, and alter the elevation of cytokines generated by NK cells in response to tumor cells.

4.2.2 Intravenous anesthetics

4.2.2.1 Etomidate

Etomidate has minimal effects on hemodynamics, therefore, it is considered for use, particularly in elderly, critically ill, and/or hemodynamically unstable patients. Due to its inhibition of the adrenal cortex, etomidate is not recommended for immunosuppressed or septic patients. Very few studies have investigated the effect of etomidate on cancer. In an in vivo study by Liu et al. [34] in 2016, it was found that etomidate significantly reduces the viability of macrophages in a dose-dependent manner.

4.2.2.2 Propofol

Propofol seems to have opposite effects to other general anesthetics as far as immunity is concerned. It seems that this drug does not suppress the immune system, but rather the opposite. It favors the cytotoxicity of NK cells, reduces the motility and invasiveness of tumor cells, inhibits COX and does not promote the synthesis of HIF (hypoxia-inducible factor), which is associated with a proven pro-angiogenic effect through the expression of vascular endothelial growth factor (VEGF) [28].

Different studies have observed beneficial anti-metastatic effects. It has been proposed that the inhibition of COX-2, and therefore of PGE2, could result in an improvement of the antitumor response of the immune system [38]. Other authors have proposed that propofol’s weak β-adrenergic antagonist mechanism could be involved in its antitumor protection since many tumor cells have β-adrenergic receptors [39].
Zheng et al. [40] published 2018 a retrospective study of patients operated on for gastric cancer between 2007 and 2012, this study included 2856 individuals divided into 2 groups. Anesthetic maintenance was performed in one group based on total intravenous anesthesia (TIVA) with propofol plus remifentanil and the other with sevoflurane and remifentanil, showing greater survival in the group of patients that used TIVA.

Inada et al. [41] observed in patients undergoing craniotomy, how inhalational anesthesia with isoflurane compared with intravenous propofol produced a decrease in the ratio of Th type 1 and 2 lymphocytes (Th1/Th2), which facilitates tumor progression, tilting the balance towards Th2 production; predominating therefore humoral immunity. On the other hand, Ren et al. [42] confirmed these findings with isoflurane versus propofol in lobectomy for lung cancer. They hypothesize that propofol promotes the activation and differentiation of peripheral Th cells to Th1, thereby favoring perioperative anti-metastatic cellular immunity.

In a study by Zhang Ye et al. [43] TIVA with propofol at therapeutic doses of 2–5 micrograms/milliliter (μg/ml) was found to inhibit tumor proliferation, induce apoptosis, and reduce invasion of osteosarcoma tumor cells (Figure 5).

4.2.2.3 Thiopental

Thiopental reduces both the number and activity of NK cells in animal models [24].

![Figure 5](image.png)

**Figure 5.**

Propofol inhibits cell proliferation, promotes apoptosis, and reduces invasion. Propofol inhibits proliferation (A), promotes apoptosis (B–C), and reduces invasion (D) of MG63 osteosarcoma cell in a dose-dependent manner. *P < 0.01 compared with the control group without propofol treatment. Image taken from the article by Zhang Ye et al. [43]. With permission of the author.
4.2.2.4 Ketamine

In a study in rats, Melamed et al. [44] determined that ketamine causes a significant decrease in the number and activity of NK cells, greater lung tumor progression as well as more numerous and aggressive lung metastases. Of the hypnotics analyzed in this study, ketamine showed the greatest immunosuppressive action, probably related to its potent adrenergic action. Recent studies support these conclusions and show not only decreased activity of neutrophils and NK cells, but also induces lymphocytic apoptosis in humans and inhibits the functional maturation of dendritic cells, interfering with other determinants of the immune reaction as in the production of cytokines that affect cellular immunity [44].

4.2.2.5 Benzodiazepines

Commonly used as anxiolytics, sedatives, anticonvulsants, and in the context of alcohol withdrawal. Among them, midazolam, lorazepam, clonazepam, and diazepam, are useful in anesthetic practice due to their properties, especially midazolam, for being a safe drug with a short half-life. The immune changes produced by the use of benzodiazepines have shown disparate results, and it has not been determined that they are drugs that produce significant variations in immunity and, therefore, in cancer recurrence. Negative results were obtained with supraphysiological concentrations, where the chemotaxis capacity was diminished; in another context, Marino et al. [45] found that single doses of diazepam and midazolam induced neutrophil migration and phagocytosis. In general, they are useful drugs in the practice of anesthesia in patients with neoplasia.

4.2.2.6 Opiates

One of the most frequent symptoms in cancer patients is pain, between 50 and 80% of patients experience some degree of pain. It is known that opiates are fundamental in the treatment of acute and chronic pain, as well as the perioperative period of oncological surgery. As the tumor progresses, it can cause severe pain related to the invasion of adjacent tissues, compromising nerves and bone structures [46].

The main concern regarding the effect that opiates may have; over the morphic in terms of oncological progression through the dissemination of tumor cells and the establishment of distant metastases, is mainly explained by 2 mechanisms; interactions with the immune system and stimulation of angiogenesis [47].

Impaired immune function is known to have a multifactorial etiology. On the one hand, the presence of uncontrolled pain generates activation of the SNS and the HPA axis with the consequent release of cortisol and catecholamines that determine immunosuppression [48]. On the other hand, there is both direct and indirect action of opioids on the immune system. Indirectly through the HPA axis and directly through specific receptors for opioids, such as µ3. These µ3 receptors and others such as OGFr (opioid growth factor receptor), are involved in cell signaling processes that mediate antibody production and NK cell-mediated cytotoxicity. The administration of opioids has been related to a decrease in the number and activity of NK cells, inhibition in the production of immunostimulatory cytokines such as IFN-γ and IL-2, less proliferation and activation of T lymphocytes, as well as less antibody production [49].
Opioids affect the integrity of the vascular endothelium, where they produce proliferation and migration of endothelial cells, a process known as angiogenesis [50]. Morphine administered in usual concentrations stimulates angiogenesis and proliferation of microvascular endothelial cells through a signaling pathway similar to that described for VEGF [51].

Binding to $\mu_3$ and OGF receptors by the synthetic opioids fentanyl and remifentanil occurs with much lower affinity [52].

Tramadol, in addition to its effect on the $\mu$ receptor, has adrenergic, serotonergic, and appears to preserve perioperative immune function compared to morphine. Studies have proposed that tramadol stimulates the activity of NK cells. Opioids with less structural similarity to morphine and less affinity for $\mu$ receptors are probably those that determine less immunosuppression [53].

Recent studies speak of a dual effect of morphine in the regulation of tumors, including its effects on proliferation, metastasis, angiogenesis, inflammation, and immunity.

In a review carried out in 2018; Tuerxun et al. [46] maintain that the main factors responsible for the dual role of morphine in terms of its activity on cancer lie in the dose and the type of tumor. In general terms; at high concentrations, morphine inhibits tumor cell growth, angiogenesis, invasion, and metastasis. However, low daily doses of morphine stimulate tumor cell proliferation, angiogenesis, and immunosuppression. Future studies will elucidate how true these claims are, but for now, they open a door to the analysis that will allow us to discuss how influential the use of morphine is in the perioperative period of cancer patients.

4.2.2.7 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit COX-1 and COX-2, a fundamental enzyme of the arachidonic acid cascade that ends with the synthesis of the different eicosanoids (prostaglandins, thromboxanes, and leukotrienes). Overexpression of the enzyme cyclooxygenase 2 (COX-2) has been found in about 90% of lung tumors, 71% of intestinal adenocarcinomas, and 56% of breast cancer neoplasms, among other types of cancer. The hyperfunctioning of this enzyme results in increased synthesis of PGE2, which inhibits NK cell activity, increases angiogenesis, and decreases cell apoptosis, favoring tumor progression [54].

The influence of prostaglandins on cancer seems to be mediated by two mechanisms. The first is an indirect mechanism through its interaction with the antitumor immune system. PGE2, synthesized by macrophages, produces a decrease in the number of NK cells with a reduction in cytotoxic activity, also affecting the response mediated by CD8+ T lymphocytes, favoring the secretion of Th2-type cytokines compared to Th1, a phenomenon that occurs in the perioperative period. The second is a direct mechanism of interaction with tumor growth and spread [55]. HIFs are intracellular proteins that coordinate the cell's adaptive response to hypoxemia, regulating genes that act to promote angiogenesis, cell proliferation, and metabolism. These proteins are closely linked to mechanisms of cellular adaptation to hypoxia, also known as hypoxic preconditioning. PGE2 has proangiogenic effects on tumor cells [56]. Taking into account the pro-tumor effects of prostaglandins, it seems logical to think that NSAIDs could have an anti-tumor effect [57].
4.2.2.8 Local anesthetics and regional anesthesia

Both local anesthetics and regional anesthetic techniques seem to have a protective action against the progression of oncological disease. The justification for this statement is based on the attenuation of the endocrine-metabolic response to surgical stress and, consequently, on the reduction of the concentrations of glucocorticoids and endogenous catecholamines. On the other hand, local anesthetics favor the increased activity of CD8+ T lymphocytes and NK cells. In addition to regional anesthesia, less invasive surgical techniques reduce stress with the eventual decrease in SNS stimulation and decrease opioid requirements with the benefits that this entails. All of the above-mentioned favor the improvement of cellular immunity and could be associated with lower rates of cancer recurrence [58, 59].

Local anesthetics exert their effect by blocking voltage-gated sodium channels in the membrane of nerve cells, which are also found in the membrane of tumor cells and are thought to be involved in tumor cell invasion and metastasis [60].

In 2014 Scavonetto et al. [61] compared general anesthesia alone versus general anesthesia combined with epidural in a retrospective study in 1642 patients undergoing radical prostatectomy. This study demonstrated that supplementing general anesthesia with neuraxial analgesia for prostate cancer surgery was associated with decreased systemic cancer progression and improved overall survival compared with general anesthesia alone. This finding cannot be used to discriminate which element of anesthetic treatment (intrathecal opioids, local anesthetics) or mechanism (reduced stress response or systemic opioid reduction) may have contributed to the apparent benefit, but it is nevertheless a promising start for further research.

Recent studies have focused on the antitumor properties of local anesthetics; Wang HW et al. [60] in a study published in 2015, investigated the influence of local anesthetics on non-small cell lung cancer and found that lidocaine and ropivacaine can inhibit cell growth, invasion, and migration carcinogens, as well as induce their apoptosis. The antitumor properties of local anesthetics offer a potential opportunity for clinical application.

4.2.2.9 Glucocorticoids

Corticosteroids are commonly used in anesthesia for the prophylaxis of postoperative nausea and vomiting. When administered in a single dose, after the start of surgery, they attenuate the inflammatory response and the pain associated with the surgical procedure [62].

Although it is known that the prolonged use of these drugs worsens the prognosis of cancer patients, it is questionable whether their use limited to the perioperative period influences tumor proliferation and the appearance of metastases. There are conflicting results. Some studies show a reduction in tumor angiogenesis, levels of VEGF, and circulating interleukins with the use of single-dose corticosteroids [63]. Singh et al. [62] showed an increase in distant metastases in colon cancer when dexamethasone was used in a single dose, concluding that further studies are still needed to define the role of these drugs in tumor recurrence.

4.2.2.10 β-adrenergic blockers

β-adrenergic receptors have been associated with the progression of neoplasms; not only because of their presence in neoplastic cells and inducing changes in the
dynamics of the immune system and tumor microenvironment, but also because they are active components of the endocrine-metabolic response and inflammation associated with surgical trauma. In an observational study carried out by Hiller et al. [64] in 2015, it was possible to demonstrate a reduction in the incidence of tumor recurrence and greater survival in patients who had indicated the use of β-adrenergic blockers. Another study carried out by Wang HM et al. [65] in 2012 concluded that β-adrenergic blockers are associated with an improvement in metastasis-free survival, disease-free survival, and overall survival in this cohort of patients with non-small cell lung cancer, who were undergoing radiotherapy. Most of the patients who had a beneficial outcome in the study were taking cardioselective β-adrenergic (β1) blockers, which is consistent with other findings indicating that β1 receptors are responsible for negative outcomes in lung adenocarcinoma.

However, there is currently little scientific evidence to support the perioperative use of these drugs to reduce the catecholaminergic response and improve cellular immunity; Therefore, these findings should be verified in future studies that guarantee their efficacy, always taking into account risk–benefit in each particular patient.

4.2.2.11 α2 adrenergic agonists

Dexmedetomidine is a potent alpha 2 adrenergic agonist that exhibits sedative, hypnotic, analgesic, and sympatholytic effects. These characteristics make it possible to reduce the use of inhalation agents, opiates, and the sympathetic response in the perioperative period, with the consequent decrease in circulating catecholamine levels [66]. Based on the fact that both the sympathetic response and the pro-inflammatory state secondary to surgery, as well as the use of morphine, have been shown to accelerate tumor progression; It is believed that dexmedetomidine could reduce the progression of neoplastic disease secondary to the modulation of the inflammatory state typical of surgery, added to the reduction in the use of opiates and inhalational anesthetics [67].

It is known that surgery can determine immunosuppression, this is of vital importance in cancer patients. Some studies have shown the role of dexmedetomidine in the immune response of cancer patients. Wang Y et al. [68] indicate that this drug maintains the Th1/Th2 ratio, which decreases the inflammatory response of patients who underwent gastric surgery with the consequent reduction in immunosurveillance alterations, which is of great importance in cancer patients. Due to the above, both in theory and in practice, dexmedetomidine is considered a very promising drug when it comes to the perioperative period of cancer patients. Unfortunately, recent studies show that this drug can promote tumor growth mainly secondary to direct stimulation of cancer cells. In an animal study, Lavon et al. [69] showed that dexmedetomidine at hypnotic doses may be related to the growth of metastases in the primary tumor of the breast, lung, and colon, although at sub hypnotic doses, that is, analgesic and sedative, the effect is not predictable; but not on all models. In addition, a study published by Gong et al. [70] showed that dexmedetomidine could negatively modulate human immunity by inhibiting the maturation and proliferation of dendritic cells, as well as by decreasing the activity and cytotoxicity of CD8+ T lymphocytes.
4.2.2.12 Statins

They have anti-inflammatory, immunomodulatory, and anti-angiogenic effect. They reduce the incidence of colon, prostate, and skin cancer. In a study by Rubin et al. [71] in 2005, a relative reduction of 47% in the risk of colorectal cancer was demonstrated.

5. Anesthetic management

Based on the latest evidence found in the literature, it is considered good anesthetic practice for resection of bone tumors to perform a TIVA based on remifentanil and

<table>
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<tr>
<th>Preoperative</th>
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<tr>
<td>Avoid Hypothermia</td>
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<td>NSAIDs</td>
<td>Inhibits COX-2</td>
<td>Reduces angiogenesis</td>
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<td>NSAIDs</td>
<td>NSAIDs Included in a regional technique, allows us to maintain an adequate analgesic blockade; and reduce the doses of major intravenous opiates such as Morphine.</td>
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<td>NSAIDs</td>
<td>NSAIDs Increases the activity of NK cells and cytotoxic T lymphocytes.</td>
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<td>Regional analgesia based on peripheral nerve blocks with local anesthetics.</td>
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<td>Dipyrone.</td>
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<td>Paracetamol.</td>
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Table 2. Perioperative strategies to reduce the risk of tumor recurrence.

propofol, in addition to adjuvant regional techniques according to the procedure to be performed (Table 2) [5]. We propose the example of a healthy young patient who undergoes resection surgery for osteosarcoma of the knee. After adequate standard ASA (American Society of Anesthesiologists) monitoring (Figure 6) [72], and monitoring of anesthetic depth through NINDEX monitor, (Figure 7) [73], the anesthetic technique that would provide the greatest benefits based on the previously mentioned; is combined general-epidural anesthesia. A propofol and remifentanil.

Figure 6. Standard ASA monitoring (American Society of Anestesiologists).

Figure 7. Anesthetic depth monitoring NINDEX (Narcosis INDEX).
TIVA, target-controlled infusion in effect-site (TCLce), plus a continuous infusion of 1% lidocaine, 1 mg/kg/hour through the epidural catheter. It is also vitally important to help with NSAIDs such as Ketoprofen.

Through this anesthetic technique, multiple objectives are achieved:

**Propofol:**

- The use of propofol at the effect site at doses between 2 and 5 μg/ml determines the apoptosis of tumor cells that could detach from the tumor that is being resected and are found in the bloodstream. This was demonstrated in a work by Zhang Ye et al. [43] in 2014.
- It is believed that this drug does not suppress the immune system. Propofol favors the cytotoxicity of NK cells, reduces the motility and invasiveness of tumor cells, inhibits COX and does not promote HIF synthesis, thus having an antiangiogenic effect.
- It has been proposed that the inhibition of COX-2, and therefore of PGE2, could result in an improvement of the antitumor response of the immune system since prostaglandins are at the base of the formation of neo vessels.
- The β-adrenergic antagonist of propofol could be involved in its antitumor protection, since many tumor cells have β-adrenergic receptors; this confers a partial blockade of the HPA axis with the consequent immunoprotective response.

**Lidocaine:**

Either in favor of opting for a regional technique that allows us to maintain an adequate analgesic blockade and allows, among other things, to reduce the dose of major intravenous opiates such as morphine, as well as for the benefits of local anesthetics per se; The use of lidocaine intraoperatively and postoperatively has great implications for tumor recurrence in cancer patients who undergo surgery. In the first place, it allows a marked reduction in plasma concentrations of cortisol and catecholamines secondary to the decrease in endocrine-metabolic responses triggered by tissue destruction related to surgery. Second, they act directly by increasing the activity of NK cells and CD8+ T lymphocytes; vital cells to maintain the integrity of cellular immunity.

**NSAIDs:**

The hyper-functioning of COX-2 secondary to its overproduction in some types of tumors; results in increased synthesis of PGE2, which inhibits NK cell activity, increases angiogenesis, and decreases cell apoptosis, favoring tumor progression. The use of COX-2 type NSAIDs reduces the synthesis of PGE2, favoring immunosurveillance with its positive effects on immunity.

### 6. Conclusions

Multiple clinical studies suggest that both anesthesia and surgery induce immunosuppression that can promote tumor recurrence through locoregional growth and distant spread; undesirable circumstance that reduces the survival of our patients and impoverishes their prognosis.
We believe that the anesthetic plan should include immunoprotective actions that fully cover the entire perioperative period. Among them we highlight minimizing the response to psychological and physiological stress, through medical stability and adequate pre, intra and postoperative analgesia.

An anesthetic-surgical technique that minimizes tissue injury, reduces bleeding and reduces the risk of blood transfusion will be beneficial in order to reduce tumor progression.

Although the evidence on the influence of anesthetic drugs on tumor progression is limited, it can be stated, based on recent experimental and clinical studies, that the use of anesthetic/analgesic techniques that reduce the perioperative consumption of opiates such as morphine, as well as other drugs with a proven negative profile, such as ketamine, are favorable to protect the anti-metastatic immune response in a period of special pro-tumor susceptibility such as the perioperative period.

We propose anesthetic techniques combined with the use of regional anesthesia and analgesia, preferring them to those based on the use of opioids and halogenated agents, since it has been shown that situations that determine greater activation of the SNS and the HPA axis, promoting a pro-inflammatory state, will generate a negative alteration of immunity with the consequent higher rate of tumor recurrence.

Therefore, based on current evidence and our experience, we recommend the use of supported analgesic/anesthetic techniques based on regional anesthetic blocks prior to surgical aggression, complemented by the administration of NSAIDs, dipyrone, paracetamol, and anesthetic maintenance with propofol. As well as an adequate management of psychological stress, the maintenance of normothermia and techniques that reduce the risk of blood transfusions in the perioperative period are related to the preservation of immunity and therefore with better results in cancer patients.

Acknowledgements

To Dr. Alejandro Corujo Núñez who carried out the revision of this chapter.

Conflict of interest

The authors declare no conflict of interest.
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