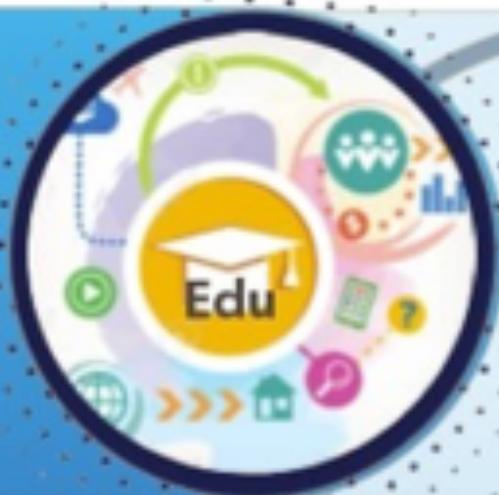




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# Perioperative Immunosuppression in Cancer Patients: impact of anes- thetic techniques

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## ABSTRACT

*Surgical stress and anesthesia are well-documented triggers of transient immunosuppression in cancer patients, potentially promoting tumor progression and metastasis during the perioperative period. Different anesthetic techniques—such as general anesthesia with volatile agents, total intravenous anesthesia (TIVA), regional blocks, and opioid-based analgesia—exert variable effects on immune function. This review summarizes current evidence on how anesthetic modalities influence cellular and humoral immunity in oncologic surgery. Key mechanisms discussed include effects on natural killer (NK) cell activity, cytokine release, neutrophil function, and regulatory T cell populations. The review also examines how these immunological changes may affect oncologic outcomes, including recurrence and survival. Understanding these effects is critical to tailoring anesthesia protocols that minimize immunosuppression and support host defense during the perioperative window.*

**Keywords:** Cancer, perioperative immunosuppression, anesthesia, TIVA, immune function, surgical oncology

## INTRODUCTION

The perioperative period in oncologic patients is characterized by profound physiological stress that affects not only hemodynamics and metabolism, but also

significantly alters immune homeostasis. Accumulating evidence suggests that surgical trauma and anesthesia can transiently impair innate and adaptive immunity, facilitating micrometastatic spread, tumor cell escape from

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immune surveillance, and ultimately influencing long-term oncologic outcomes [1,2]. This phenomenon—termed perioperative immunosuppression—has become a focus of considerable clinical and translational research, particularly in light of emerging data that connect anesthetic technique to recurrence and survival in cancer patients.

The perioperative window is now recognized as a critical immunological interval, during which circulating tumor cells (CTCs) may be mobilized, and minimal residual disease can proliferate under the radar of a temporarily weakened immune system [3]. The immune system's key effector components—especially natural killer (NK) cells, cytotoxic T lymphocytes, and macrophages—are suppressed to varying degrees by surgical stress, opioid use, and certain anesthetic agents. Simultaneously, an increase in immunosuppressive pathways, including the expansion of regulatory T cells (Tregs) and the upregulation of inhibitory cytokines such as IL-10 and TGF- $\beta$ , contributes to a tumor-permissive environment [4].

Anesthetic technique appears to play a pivotal role in modulating these immune alterations. Volatile agents such as sevoflurane and isoflurane have been implicated in suppressing NK cell function and altering cytokine release profiles, whereas total intravenous anesthesia (TIVA) with propofol is associated with more favorable immunomodulatory effects [5]. Similarly, regional anesthesia—whether spinal, epidural, or paravertebral—has shown potential in attenuating the neuroendocrine stress response, reducing opioid requirements, and preserving immune competence [6]. The use of opioids, while essential for analgesia, may further depress cellular immunity and has been associated with increased cancer recurrence in some retrospective studies [7].

Given the increasing complexity of oncologic surgery and the expanding array of anesthetic options, there is a pressing need to elucidate how specific anesthetic protocols influence perioperative immune dynamics. Moreover, identifying strategies to mitigate immunosuppression could improve not only immediate postoperative recovery but also long-term cancer outcomes.

This review aims to critically examine the impact of different anesthetic techniques on perioperative immune function in cancer patients. It will explore the underlying immunological mechanisms, evaluate the existing clinical and experimental evidence, and discuss the potential implications for anesthetic planning and perioperative oncologic care. In doing so, it seeks to support the de-

velopment of immunologically informed anesthesia protocols that balance surgical requirements with the imperative to preserve antitumor immunity.

## **1. Mechanisms of Perioperative Immunosuppression in Cancer Surgery**

The immunological milieu of the perioperative period is shaped by a complex interplay of neuroendocrine, inflammatory, and pharmacologic factors that collectively suppress the host's ability to mount effective antitumor responses. This transient yet clinically significant immunosuppression is of particular concern in oncologic patients, where residual tumor cells and circulating tumor cells (CTCs) may exploit the weakened immune environment to establish micrometastases or promote recurrence [8].

Surgical trauma is a principal trigger of immunosuppressive cascades. Tissue injury activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, leading to a systemic release of glucocorticoids and catecholamines. These hormones directly inhibit T-cell proliferation and reduce the cytotoxic activity of natural killer (NK) cells—key players in controlling tumor spread [9]. In addition, elevated levels of proinflammatory cytokines, such as IL-6, TNF- $\alpha$ , and CRP, induce a shift toward an anti-inflammatory response, marked by increased levels of IL-10 and transforming growth factor-beta (TGF- $\beta$ ), which suppress dendritic cell maturation and enhance the expansion of regulatory T cells (Tregs) [10].

This shift in cytokine balance contributes to a decline in cell-mediated immunity, including reduced Th1/Th2 ratio, impaired antigen presentation, and diminished cytotoxic T lymphocyte (CTL) responses. Notably, studies have shown that perioperative suppression of NK cell function correlates with higher tumor burden and reduced progression-free survival in several malignancies, including breast, colorectal, and lung cancers [11].

Anesthetic agents further modulate these immunological dynamics. Inhalational anesthetics, such as isoflurane and sevoflurane, have been shown in both in vitro and in vivo models to suppress NK cell cytotoxicity, reduce T-cell proliferation, and promote angiogenesis through upregulation of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and vascular endothelial growth factor (VEGF) [12]. These effects may contribute to an immunosuppressive tumor microenvironment and facilitate cancer progression.

Opioids, widely used for intraoperative and postoperative analgesia, also exhibit immunosuppressive properties. Morphine and other  $\mu$ -opioid receptor agonists impair NK cell activity, reduce macrophage phagocytosis, and modulate the cytokine milieu in favor of tumor survival [13]. Moreover, opioid-induced inhibition of gastrointestinal motility and endocrine dysfunction may exacerbate stress responses, further undermining host defenses.

In contrast, propofol-based total intravenous anesthesia (TIVA) appears to exert protective immunologic effects. Propofol has been associated with preservation of NK cell function, suppression of proinflammatory cytokine surges, and inhibition of cancer cell migration and invasion in preclinical models [14]. These findings have spurred interest in TIVA as an oncologically favorable anesthetic strategy, although randomized clinical trials are ongoing to confirm survival benefits.

Additionally, the neuroendocrine modulation of immune function plays a crucial role.  $\beta$ -adrenergic signaling, activated by catecholamine release during surgery, promotes tumor cell proliferation, inhibits apoptosis, and enhances matrix metalloproteinase activity. This has led to exploration of perioperative  $\beta$ -blockade as a means of reducing surgical immunosuppression and limiting tumor dissemination [15].

Taken together, the mechanisms of perioperative immunosuppression are multifaceted, involving direct effects of surgical trauma, endocrine activation, and anesthetic pharmacology. Their convergence in the perioperative setting may create a transient but critical window during which tumor control is compromised, highlighting the need for anesthetic strategies that preserve immune competence and support oncologic outcomes.

## **2. Immunomodulatory Effects of Different Anesthetic Techniques**

The choice of anesthetic technique is increasingly recognized as a modifiable factor influencing perioperative immune function and, by extension, long-term oncologic outcomes. Although the primary goal of anesthesia is to ensure analgesia, amnesia, and hemodynamic stability, accumulating evidence suggests that anesthetics may exert immunomodulatory effects, both beneficial and detrimental, depending on their pharmacodynamic profile and route of administration.

Volatile inhalational anesthetics, such as isoflurane, sevoflurane, and desflurane, have been shown to impair immune surveillance through multiple mechanisms. Ex-

perimental studies demonstrate that these agents suppress natural killer (NK) cell cytotoxicity, reduce T lymphocyte proliferation, and promote a shift toward Th2-dominated immune responses [16]. Furthermore, volatile agents increase the expression of hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) and vascular endothelial growth factor (VEGF), facilitating angiogenesis and potentially enhancing tumor cell survival and metastasis [17]. In animal models, exposure to isoflurane has been linked to accelerated growth of breast and colorectal cancer xenografts, suggesting a tumor-promoting role of inhalational agents [18].

In contrast, total intravenous anesthesia (TIVA), particularly when administered with propofol, appears to preserve or even enhance perioperative immune competence. Propofol possesses antioxidant and anti-inflammatory properties, stabilizes the mitochondrial membrane, and reduces the production of proinflammatory cytokines such as IL-6 and TNF- $\alpha$  [19]. Importantly, propofol has been reported to maintain NK cell activity and reduce cancer cell adhesion and migration in vitro [20]. Retrospective clinical data support these findings, with several studies suggesting a lower recurrence rate and improved survival in patients undergoing oncologic surgery under TIVA compared to volatile anesthesia [21]. However, prospective randomized trials are still underway to validate these observations.

Regional anesthesia and analgesia, including epidural, spinal, and paravertebral blocks, offer additional immune-preserving benefits. By attenuating the neuroendocrine stress response to surgery and reducing systemic opioid requirements, regional techniques contribute to a more favorable perioperative immunologic profile [22]. For instance, thoracic epidural analgesia has been associated with preserved NK cell activity and lower circulating levels of catecholamines and cortisol, factors known to suppress immune function [23]. Moreover, some studies have linked regional anesthesia with reduced metastasis rates in breast and prostate cancer surgery, although the data remain heterogeneous [24].

The use of opioids remains central to perioperative analgesia, but their immunosuppressive effects are a growing concern in oncologic contexts. Morphine, fentanyl, and other  $\mu$ -opioid receptor agonists inhibit lymphocyte proliferation, impair macrophage and neutrophil function, and downregulate NK cell cytotoxicity [25]. These effects are dose-dependent and may be amplified in patients undergoing prolonged procedures or receiving high-dose postoperative opioids. The introduction

of multimodal analgesia—combining non-opioid analgesics such as NSAIDs, acetaminophen, and local anesthetics—has helped reduce opioid consumption and mitigate immunosuppression [26].

Other agents, such as ketamine, dexmedetomidine, and lidocaine, have also been investigated for their immunomodulatory potential. Ketamine has shown both pro- and anti-inflammatory effects depending on dose and context, while dexmedetomidine appears to reduce sympathetic activity and preserve T-cell function [27]. Intravenous lidocaine, used perioperatively for analgesia and anti-inflammatory purposes, has been associated with improved postoperative recovery and potentially enhanced immune function, though oncologic implications remain under investigation [28].

In summary, anesthetic technique exerts a significant and measurable influence on perioperative immune dynamics. TIVA and regional anesthesia appear to offer the most favorable immunologic profiles, while volatile agents and opioids may compromise host defense. As our understanding of these effects deepens, there is growing support for the strategic selection of anesthetic regimens that minimize immunosuppression, particularly in patients with active malignancy or high metastatic risk.

### CONCLUSION

The perioperative period in cancer surgery represents a vulnerable window during which host immune function is often compromised, potentially facilitating tumor progression and metastasis. Increasing evidence highlights the significant role that anesthetic technique plays in modulating perioperative immune responses. Volatile anesthetics and opioids, though essential in many contexts, may contribute to immunosuppression and adversely impact oncologic outcomes. Conversely, propofol-based total intravenous anesthesia (TIVA) and regional anesthesia techniques appear to preserve innate and adaptive immunity, offering potential advantages for tumor control and long-term survival.

Given the increasing complexity of surgical oncology and the expanding therapeutic landscape, anesthesiologists must consider not only the hemodynamic and analgesic profile of anesthetic agents but also their immunological effects. Future research, including well-designed randomized controlled trials, will be essential to validate existing data and inform clinical guidelines.

Ultimately, the integration of immunological principles into anesthetic planning represents a promising strategy to enhance perioperative care and improve can-

cer-related outcomes. Personalized anesthesia protocols tailored to individual oncologic risk may become a key component of comprehensive cancer therapy in the modern surgical era.

### Conflict of Interest

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## **ONKOLOGIK BEMORLARDA PERIOPERATION IMMUNOSUPRESSIYA: ANESTEZIOLOGIK YONDASHUVLARNING TA’SIRI**

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### **ANNOTATSIYA**

Jarrohlik stressi va anesteziya onkologik bemorlarda vaqtinchalik immunosupressiyani yuzaga keltirishi mumkin, bu esa perioperatsion davrda o’sma rivojlanishi va metastazlanishini kuchaytiradi. Har xil anesteziologik yondashuvlar – uchuvchi anestetiklar, umumiy vena orqali anesteziya (TIVA), regional blokklar va opioiddga asoslangan analgeziya – immun tizimga turlicha ta’sir qiladi. Ushbu maqolada saraton jarrohligida ishlatiladigan anesteziya usullarining hujayraviy va gummoral immunitetga ta’siri bo’yicha hozirgi dalillar umumlashtiriladi. NK hujayralari faolligi, sitokinlar ajralishi, neytrofillar funksiyasi va T-regulyator hujayralar soniga ta’sir mexanizmlari yoritilgan. Shuningdek, ushbu immunologik o’zgarishlarning qaytalanish va omon qolish kabi onkologik natijalarga ta’siri muhokama qilinadi. Immunitetni qo’llab-quvvatlaydigan anesteziya protokollarini ishlab chiqish saraton jarrohligida muhim ahamiyat kasb etadi.

**Kalit so’zlar:** Saraton, perioperatsion immunosupressiya, anesteziya, TIVA, immun funktsiya, jarrohlik onkologiyasi

## **ПЕРИОПЕРАЦИОННАЯ ИММУНОСУПРЕССИЯ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: ВЛИЯНИЕ АНЕСТЕЗИОЛОГИЧЕСКИХ ПОДХОДОВ**

**Хамдамов Б.З., Ибрагимов Н.К., Рахимов Б.А.**

### **АННОТАЦИЯ**

Хирургический стресс и анестезия являются известными триггерами транзиторной иммуносупрессии у онкологических пациентов, что может способствовать прогрессированию опухоли и метастазированию в периоперационном периоде. Различные анестезиологические подходы — ингаляционные анестетики, тотальная внутривенная анестезия (TIVA), регионарные блокады и опиоидная анальгезия — по-разному влияют на иммунную систему. В статье обобщены современные данные о влиянии различных методов анестезии на клеточный и гуморальный иммунитет в онкологической хирургии. Рассматриваются ключевые механизмы: активность NK-клеток, продукция цитокинов, функция нейтрофилов и популяции регуляторных T-клеток. Также анализируются потенциальные последствия этих иммунных изменений для онкологических исходов, включая рецидивирование и выживаемость. Понимание этих эффектов критично для разработки анестезиологических протоколов, минимизирующих иммуносупрессию в периоперационном окне.

**Ключевые слова:** Рак, периоперационная иммуносупрессия, анестезия, TIVA, иммунитет, онкологическая хирургия