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Correction of Perioperative Immunosuppression in Cancer Patients: current approaches and future perspectives

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ABSTRACT

The immunosuppressive effects of surgical trauma, anesthesia, and opioid use in the perioperative period may compromise antitumor immunity in cancer patients, potentially promoting metastasis and recurrence. Strategies to correct or mitigate perioperative immunosuppression are gaining importance in oncologic anesthesiology. This review summarizes current and emerging approaches to support immune function in the perioperative setting. These include pharmacologic interventions (e.g., COX-2 inhibitors, β-blockers, dexmedetomidine), anesthetic technique modification (e.g., regional anesthesia, TIVA), immune-modulating nutrition, and perioperative immunotherapy. Mechanistic insights into immune restoration, timing of interventions, and clinical outcomes are critically discussed. The review advocates for the implementation of personalized, immunologically informed perioperative care protocols to enhance oncologic outcomes.

Keywords: *Cancer, perioperative period, immunosuppression, immune correction, beta-blockers, dexmedetomidine, anesthesia, surgical oncology*

INTRODUCTION

The perioperative period in oncologic surgery represents a critical window during which systemic immune function can be markedly suppressed by a combination of surgical trauma, neuroendocrine activation, anesthetic exposure, and opioid administration. While these physiological responses are evolutionarily conserved mechanisms aimed at limiting inflammation and facilitating tissue repair, they may have unintended oncological consequences, particularly in cancer patients with circulating tumor cells or minimal residual disease [1,2]. Numerous experimental and clinical studies suggest that this transient immunosuppressive state facilitates tumor cell survival, migration, and metastasis, potentially contributing to disease recurrence and poorer long-term outcomes [3].

Key components of the host's antitumor immunity, including natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), and antigen-presenting dendritic cells, are

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functionally impaired in the early postoperative period. This immunosuppression is mediated by elevated levels of glucocorticoids and catecholamines, reduced expression of cytotoxic effector molecules, and increased populations of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [4]. These changes collectively create a permissive microenvironment for micrometastatic proliferation and immune evasion.

Efforts to understand and correct perioperative immunosuppression have gained considerable traction in recent years. Multiple pharmacologic agents—including cyclooxygenase-2 (COX-2) inhibitors, β-adrenergic blockers, and alpha-2 agonists—have shown immunorestorative potential in both preclinical and early-phase clinical studies [5,6]. Simultaneously, anesthetic techniques such as propofol-based total intravenous anesthesia (TIVA) and regional anesthesia have been associated with better preservation of immune surveillance, particularly through their ability to attenuate the neuroendocrine stress response and reduce systemic inflammation [7].

In addition to pharmacologic modulation, immune-targeted nutritional support and perioperative immunotherapy are emerging as viable adjuncts for restoring immune homeostasis. Immunonutrition, with arginine, glutamine, and omega-3 fatty acids, has been shown to enhance T-cell proliferation, cytokine balance, and wound healing in cancer surgery patients [8]. Meanwhile, the concept of "perioperative oncologic immunotherapy"—including checkpoint inhibition or cytokine support during the perioperative phase—is being actively explored in clinical trials, aiming to maintain immunosurveillance during this vulnerable period [9].

Despite the promise of these approaches, their clinical adoption remains limited, often due to fragmented protocols, limited awareness among clinicians, and insufficient randomized controlled trial data. As immuno-oncology continues to evolve, the perioperative period must be viewed not only as a time of surgical risk but also as an opportunity for targeted immunological intervention that may influence long-term cancer control.

This review aims to consolidate current knowledge on the correction of perioperative immunosuppression in cancer patients, highlighting both established and experimental strategies. By examining their mechanisms of action, timing of administration, and effects on clinical outcomes, we seek to provide a comprehensive overview that supports the development of personalized perioperative protocols grounded in immunological principles.

1. MECHANISMS OF IMMUNOSUPPRESSION AND RATIONALE FOR CORRECTION IN THE PERIOPERATIVE WINDOW

The perioperative phase of oncologic surgery is characterized by profound physiological and immunological shifts that can compromise the host's antitumor defense mechanisms. This transient yet clinically relevant state of immunosuppression is primarily driven by the surgical stress response, which activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, resulting in elevated systemic concentrations of cortisol, catecholamines, and proinflammatory cytokines [10].

These neuroendocrine mediators exert pleiotropic effects on immune function. Cortisol inhibits antigen presentation, reduces cytokine production by Th1 lymphocytes, and suppresses natural killer (NK) cell cytotoxicity. Catecholamines further suppress NK cells and cytotoxic T lymphocytes (CTLs) via β-adrenergic receptor signaling, while also promoting angiogenesis and tumor cell migration through enhanced secretion of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) [11]. Simultaneously, an increase in immunoregulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) creates a tolerogenic environment that favors tumor cell evasion and micrometastatic seeding [12].

These immune perturbations are not merely theoretical concerns. Clinical and experimental data consistently show that NK cell activity declines sharply within hours after surgery, correlating with increased rates of metastasis and reduced survival in animal models of breast, lung, and colon cancer [13]. Similar findings have been observed in human studies, where lower perioperative NK cell activity is associated with early relapse, especially in high-risk malignancies [14].

Given the predictable timing and reversibility of this immunosuppressive state, the perioperative window is increasingly viewed as a therapeutic opportunity. The goal is to interrupt the immunosuppressive cascade through pharmacological, nutritional, or anesthetic strategies that either preserve or restore immune function. Ideally, such interventions should be initiated preoperatively or intraoperatively, when tumor cells are most vulnerable and the immune system can be primed for effective surveillance.

Moreover, as immune checkpoint inhibitors and other immunotherapies become standard in oncologic care, preserving functional immunity during the perioperative

period may be critical to sustaining their efficacy. For instance, T-cell exhaustion or NK cell depletion may attenuate response to neoadjuvant or adjuvant immunotherapy and limit its durability [15]. Thus, immune protection is not only relevant to surgical recovery but may also enhance synergy with systemic oncologic treatments.

In light of this mechanistic understanding, perioperative immune correction strategies aim to blunt the deleterious neuroendocrine-immune cross-talk, sustain innate immune effector function, and limit the tumor-permissive milieu that surgery and anesthesia may otherwise exacerbate. These goals form the rationale for targeted perioperative interventions—pharmacological, nutritional, and procedural—that will be discussed in the following sections.

2. PHARMACOLOGIC AND ANESTHETIC STRATEGIES FOR IMMUNE SUPPORT

The recognition that surgery-induced immunosuppression can promote tumor progression has prompted interest in pharmacological agents and anesthetic techniques capable of modulating this response. A growing body of experimental and clinical evidence supports several perioperative strategies aimed at preserving immune function and mitigating the oncologic risks associated with immune dysfunction.

Among the most extensively studied agents are β-adrenergic blockers, particularly propranolol, which antagonize the effects of catecholamines released during surgical stress. Preclinical studies have demonstrated that perioperative β-blockade reduces tumor cell adhesion, angiogenesis, and metastasis in murine models [16]. Clinically, β-blockers have been associated with preservation of NK cell activity and a reduced incidence of recurrence in breast and colorectal cancer patients undergoing surgery [17]. Their ability to dampen sympathetic nervous system activation makes them a logical adjunct in the immunoprotective perioperative armamentarium.

In parallel, cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, have gained interest for their anti-inflammatory and antiangiogenic properties. COX-2 expression is upregulated in many tumors and is further increased in the surgical setting, promoting prostaglandin E2 (PGE2) production and immunosuppressive signaling [18]. By inhibiting PGE2, COX-2 inhibitors have been shown to enhance dendritic cell function, augment CTL responses, and suppress MDSC activity. When combined with β-blockers, they exhibit synergistic effects in preclinical cancer models, prompting calls for prospective trials in human surgical oncology [19].

Dexmedetomidine, an α2-adrenergic agonist, is increasingly used for sedation and sympatholytic effects. While concerns exist regarding potential immunosuppression at high doses, recent studies suggest that low-dose dexmedetomidine may preserve immune cell viability and promote a balanced cytokine profile [20]. Its ability to reduce opioid consumption and attenuate the neuroendocrine stress response supports its role in immunoconscious perioperative care, although further research is warranted.

Intravenous lidocaine, administered as a perioperative infusion, has been shown to reduce proinflammatory cytokine levels and preserve gut barrier integrity, which indirectly supports immune competence. Though its direct immunomodulatory effects are modest, lidocaine contributes to opioid-sparing analgesia, itself a key goal in reducing immune suppression [21].

The choice of anesthetic technique is equally consequential. Total intravenous anesthesia (TIVA) with propofol has demonstrated superior preservation of NK cell activity, reduced oxidative stress, and inhibition of pro-metastatic signaling pathways compared to inhalational agents [22]. Propofol also inhibits cyclooxygenase activity and downregulates HIF-1α and VEGF, key factors in the hypoxia-driven tumor microenvironment [23]. Multiple retrospective studies have suggested improved survival in patients undergoing oncologic surgery with TIVA, although ongoing randomized trials are needed for definitive conclusions.

In contrast, volatile anesthetics, such as sevoflurane and isoflurane, have been associated with suppression of immune function, upregulation of angiogenesis, and facilitation of epithelial-to-mesenchymal transition (EMT) in cancer cells [24]. While their use remains widespread, growing awareness of their potential immunosuppressive effects has led some institutions to preferentially adopt TIVA protocols in high-risk cancer cases.

Importantly, the reduction of perioperative opioid use remains a cornerstone of immune preservation. Multimodal analgesia strategies combining NSAIDs, acetaminophen, gabapentinoids, local anesthetics, and nerve blocks allow for effective pain control while minimizing the immunosuppressive burden of high-dose opioids [25].

In summary, a range of pharmacological and anesthetic interventions show promise in correcting perioperative immunosuppression in cancer patients. These

strategies, when appropriately combined and personalized, have the potential to transform perioperative management from a passive to a proactive, immune-supportive paradigm that aligns with modern principles of surgical oncology.

CONCLUSION

The correction of perioperative immunosuppression represents a pivotal challenge and opportunity in the surgical care of cancer patients. A growing body of evidence has confirmed that surgical stress, anesthesia, and opioid analgesia significantly impair host immune defenses during a critical period of vulnerability, potentially facilitating tumor recurrence and metastasis. However, this period also provides a unique window for targeted immunological intervention, aimed at preserving immune competence and enhancing oncologic outcomes.

Pharmacologic agents such as β-blockers, COX-2 inhibitors, dexmedetomidine, and lidocaine have demonstrated immunomodulatory effects that may translate into clinical benefit. Similarly, the adoption of propofol-based TIVA, regional anesthesia, and opioid-sparing analgesia aligns with emerging strategies for immunoprotection. When integrated into perioperative protocols, these measures have the potential not only to optimize short-term recovery but also to support long-term cancer control.

Future efforts must focus on conducting robust clinical trials to validate these approaches, developing biomarkers for individualized immuno-monitoring, and promoting interdisciplinary collaboration between oncologists, anesthesiologists, and surgeons. As immunotherapy becomes increasingly central in cancer care, immunologically informed perioperative management will be essential to realize its full potential.

Conflict of Interest

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ONKOLOGIK BEMORLARDA PERIOPERATSION IMMUNOSUPRESSIYANI KORREKSIYALASH: MAVJUD YONDASHUVLAR VA ISTIQBOLLAR

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ANNOTATSIYA

Jarrohlik stressi, anesteziya va opioidlar bilan bog‘liq immunosupressiya saraton bilan og‘rigan bemorlarda antitumor immunitetni susaytiradi va metastaz hamda qaytalanish xavfini oshiradi. Ushbu maqolada perioperatsion davrda immun funksiyani qo‘llab-quvvatlashga qaratilgan mavjud va istiqbolli yondashuvlar ko‘rib chiqiladi. Farmakologik vositalar (β-blokatorlar, COX-2 ingibitorlari, dekmedetomidin), anesteziya usullarining tanlovi (TIVA, regional anesteziya), immunoovqatlanish va immunoterapiya imkoniyatlari muhokama qilinadi. Ularning immunologik mexanizmlari, qo‘llash vaqti va klinik natijalarga ta’siri ilmiy jihatdan tahlil qilinadi. Shuningdek, shaxsiylashtirilgan, immunologik asoslangan perioperatsion protokollarni joriy qilish zarurligi asoslanadi.

Kalit so‘zlar: Saraton, perioperatsion davr, immunosupressiya, immun korektsiya, β-blokatorlar, dekmedetomidin, anesteziya, onkologik jarrohlik

КОРРЕКЦИЯ ПЕРИОПЕРАЦИОННОЙ ИММУНОСУПРЕССИИ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: СОВРЕМЕННЫЕ ПОДХОДЫ И ПЕРСПЕКТИВЫ

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АННОТАЦИЯ

Иммуносупрессивное воздействие хирургического стресса, анестезии и опиоидной терапии в периоперационном периоде может нарушать противоопухолевый иммунитет у онкологических пациентов и способствовать рецидиву и метастазированию. В статье рассмотрены актуальные и перспективные подходы к коррекции иммунной дисфункции в этом критическом периоде. Обсуждаются фармакологические стратегии (β-блокаторы, ингибиторы ЦОГ-2, дексмедетомидин), выбор анестезии (TIVA, регионарные методы), роль иммунопитания и возможности иммунотерапии. Особое внимание уделяется механизмам действия, времени назначения и их влиянию на клинические исходы. Подчёркивается необходимость внедрения персонализированных, иммунологически обоснованных протоколов периоперационного ведения в онкохирургии.

Ключевые слова: Рак, периоперационный период, иммуносупрессия, иммунная коррекция, β-блокаторы, дексмедетомидин, анестезия, онкологическая хирургия