

# Immune response in patients with cancer pain

---

**Golubović, Vesna; Golubović, Snježana; Sotošek-Tokmadžić, Vlatka;  
Mrakovčić-Šutić, Ines**

Source / Izvornik: **Periodicum biologorum, 2009, 111, 223 - 225**

**Journal article, Published version**

**Rad u časopisu, Objavljena verzija rada (izdavačev PDF)**

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:198144>

Rights / Prava: [Attribution 4.0 International](#)/[Imenovanje 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-10-02**



Repository / Repozitorij:

[Repository of the University of Rijeka, Faculty of  
Medicine - FMRI Repository](#)





## Immune response in patients with cancer pain

VESNA GOLUBOVIĆ<sup>1</sup>  
SNJEŽANA GOLUBOVIĆ<sup>1</sup>  
VLATKA SOTOŠEK-TOKMADŽIĆ<sup>1</sup>  
INES MRAKOVČIĆ-ŠUTIĆ<sup>2</sup>

<sup>1</sup> Department of Anesthesiology and Intensive Therapy  
Clinical Hospital Centre Rijeka,  
University of Rijeka  
Braće Branchetta 20, 51000 Rijeka, Croatia

<sup>2</sup> Department of Physiology and Immunology  
Medical Faculty, University of Rijeka, Rijeka  
Braće Branchetta 20, 51000 Rijeka, Croatia

### Correspondence:

Vesna Golubović  
Department of Anesthesiology and Intensive Therapy  
Clinical Hospital Rijeka, University of Rijeka  
Krešimirova 42, 51000 Rijeka, Croatia  
E-mail: vesna.golubovic@ri.htnet.hr

**Key words:** Immune response, pain treatment, cancer pain

### Abstract

*The role of perioperative pain management techniques on immune functions in patients with malignancies is still poorly understood. Although the suppression of cellular and humoral immune response in carcinoma patients is a subject of great scientific interest, we know very little about the changes in innate immunity (natural killer T cells-NKT cells, regulatory T cells-Tregs) following tumor growth, as well as in acquired immunity and cytotoxic functions of NK cells in these patients undergoing surgery and the involvement of different perioperative analgesia techniques. Immune compromise could affect the healing processes, postoperative infections and rate and size of tumor metastases disseminated during operation and may be associated with increased risk of mortality. Immunosuppression is also a result of perioperative psychological and physiological stress induced by the mechanisms closely related to hypothalamus-pituitary-adrenocortical axis, sympathetic nervous system, cytokines, opioids and T cell signal molecule. Furthermore, peripheral and central immune reaction play a key role in hyperalgesia and allodynia, as a consequence of releasing proinflammatory cytokines (PIC) from activated microglia and astrocytes. Release of PIC causes the augmented secretion of excitatory neurotransmitters from synaptic nerves of primary afferent neuron, representing PIC as very important mediators of enhanced pain in the periphery and in the central nervous system. These findings emphasize that perioperative pain management in patients with malignancies is significant to attenuate developed serious immune suppression mediated by the complicated network of neuro-immuno-endocrine interactions caused by the primary disease accompanied with exogenous and endogenous stimuli.*

### INTRODUCTION

Perioperative pain management is one of the most important difficulties that confront surgical patients. Inappropriate pain control may result in a higher incidence of chronic postoperative pain with prolonged hospitalization, augmented postsurgical morbidity and mortality, health care costs, as well as unnecessary suffering of patients (1). Cancer patients represent some of the most sensitive patients for pain control, regarding surgical stress with accompanied suppression of humoral and cellular immunity and diminished number and function of T lymphocytes and natural killer (NK) cells (2). Immunosuppression during the perioperative period may be the consequences of opioids and other anaesthetic agents, surgery, blood transfusion, pain, psychological stress and temperature changes, as well as the enhancement of tumor metastasis in experimental conditions (3), which suggests that adequate treatment of surgically mediated stress may even help to avoid immunosuppressive effects and represent a protective mechanism

against the metastatic diffusion after cancer surgery (4). Pain can induce neural circuits in the brain and activate brain-controlled pathways to the periphery mediated by hypothalamo-pituitary-adrenal axis and sympathetic nervous system. Neurotransmitters and hormones from these pathways bind receptors which are expressed by immune cells and organs and therefore have the ability to regulate immune response. Overproduction of cortisol additionally leads to cellular immunosuppression (5). Today, the involvement of glia cells in causing pain is marked and drugs which have the possibility of activating glia cells represent powerful mechanisms to induce pain (6).

### The role of perioperative pain management techniques on innate and acquired immune response in patients with cancer pain

The immune system distinguishes between multifactor stimuli that allow reaction or rejection to the immunological response. Natural killer (NK) and NK T (NKT) cells are important in innate immune defense. Generally, the appearance of such cells was associated with antitumor and allergic immune response, chronic inflammatory conditions, viral infections and autoimmune diseases. These cells have the unique capacity to rapidly produce large amounts of both T helper: Th1 and Th2 cytokines (7–10). Regulatory T (Treg) cells have active suppression mode and may induce peripheral tolerance (11).

Many cancer-related symptoms (pain, sleep disturbance, fatigue, cognitive dysfunction, etc) are connected with the release of proinflammatory cytokines. These cytokines: interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ) are released as a part of immune response and may cause a syndrome called sickness behavior which includes depression, lethargy, anorexia, fever, energy conservation, hyperalgesia, etc. (12, 13). It is proposed that cancer-related symptom and the cytokine-induced sickness behavior that develop in animals after the administration of infections or inflammatory agents or proinflammatory cytokines share common cytokine-based neuroimmunologic mechanisms. Cytokines are able to induce signaling that activates glial cells. This interaction is part of an immune network of injury and host that can lead to the development or facilitation of cytokine-related symptoms and pain / depression (14).

During perioperative pain management opioids has shown their immunosuppressive effects. Acute, as well as chronic administration of opioids decreases lymphoproliferation, natural killer (NK) activity, macrophage functions, and the production of interferon-gamma (IFN- $\gamma$ ) and interleukin-2 (IL-2) in experimental animals (15). Opioid administration has been associated with increased susceptibility of animals to bacterial and viral infections, and with decreased survival in tumor-bearing animals. Similar effects have been shown in humans, where data suggest that opioids may have an adverse impact on the immune system (16).

Recently many papers advocate regional anesthesia techniques instead of general anesthesia in carcinoma patients elected for surgery. Regional anesthesia is usually achieved with a combination of local anesthetics and opioids, so the total amount of opioids is reduced regarding general anesthesia as well as their adverse effects on the immune system. Local anesthetics also show anti-inflammatory properties that contribute to better pain control (17). Hong JY and Lim KT 2008 (18) showed that pre-emptive epidural analgesia can affect the perioperative immune responses and influence cancer management. Moreover, this analgesia technique is a good method of potentially controlling perioperative immune response and preventing postoperative pain in carcinoma patients.

Aristomenis *et al.* 2008 (19) in a retrospective study suggests that paravertebral anesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis during the initial years of follow-up. Biki *et al.* 2008 (20) compared anesthesia techniques for radical prostatectomy and indicate that the epidural plus general anesthesia group had an estimated 57% (95% confidence interval), 17–78% lower risk of cancer recurrence compared with the general anesthesia plus opioids group, with a corresponding hazard ratio of 0.43 (95% confidence interval).

If we compare the effects on immune responses of morphine and of the atypical opioid analgesic, tramadol, given for postoperative pain, some interesting findings exist. Tramadol and morphine showed similar analgesic function, although tramadol induced an improvement of postoperative immunosuppression and may be preferred to morphine for the treatment of postoperative pain. Morphine and tramadol share the common opioid mechanism of function, but the affinity of tramadol for  $\mu$ -opioid receptors is lower than that of morphine. On the other hand the antinociceptive effects of tramadol are mediated via a separate, nonopioid mechanism, mediated by the inhibition of neuronal uptake of noradrenaline and serotonin. Maybe these differences are the reason for the diverse pharmacodynamic profile of morphine and tramadol on immune functions (21, 22).

### CONCLUSION

Innate and acquired immune responses play a key role in host defense. Patients with malignant diseases have diminished immune functions that can be modulated by surgical stress, pain, tissue injury and invasive microorganisms which can lead to augmented susceptibility to postoperative infections and therefore difficulties in postoperative recovery. A good choice of perioperative pain management techniques plays an important role in the immune response of patients with malignancies. Prospective trials evaluating the effects of regional analgesia and opioid sparing on cancer recurrence seem warranted.

*Acknowledgment:* This work was supported by grants from the Croatian Ministry of Science (projects no: 0620096-0094 and 0620096-0092).

## REFERENCES

1. WIESELER-FRANK J, MAIER S F, WATKINS L R 2005 Immune-to-brain communication dynamically modulates pain: physiological and pathological consequences. *Brain Behav Immun* 19 (2): 104–11
2. VALLEJO R, HORD E D, BARNA S A, SANTIAGO-PALMA J, AHMED S 2003 Perioperative immunosuppression in cancer patients. *J Environ Pathol Toxicol Oncol* 22(2): 139–46
3. FRANCHI S, PANERAI A E, SACERDOTE P 2007 Buprenorphine ameliorates the effect of surgery on hypothalamus-pituitary-adrenal axis, natural killer cell activity and metastatic colonization in rats in comparison with morphine or fentanyl treatment. *Brain Behav Immun* 21 (6): 767–74
4. SACERDOTE P 2008 Opioid-induced immunosuppression. *Curr Opin Support Palliat Care* 2(1): 14–8
5. OGAWA K, HIRAI M, KATSUBE T, MURAYAMA M, HAMA-GUCHI K, SHIMAKAWA A T, NARITAKE Y, HOSOKAWA T, KAJIWARA T 2000 Suppression of cellular immunity by surgical stress. *Surgery* 127 (3): 329–36
6. WATKINS L P, MILIQAN F D, MAIER S F 2003 Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. *Adv Exp Med Biol* 521: 1–21
7. CHANG D H, OSMAN K, CONNOLLY J, KUKREJA A, KRASOVSKY J, PACK M, HUTCHINSON A, GELLER M, LIU N, ANNABLE R, SHAY J, KIRCHHOFF K, NISHI N, ANDO Y, HAYASHI K, HASSOUN H, STEINMAN R M, DHODAPKAR M V 2005 Sustained expansion of NKT cells and antigen-specific T cells after injection of [alpha]-galactosyl-ceramide loaded mature dendritic cells in cancer patients. *J Exp Med* 201 (9): 1503–17
8. MERCER J C, RAGIN M J, AUGUST A 2005 Natural killer T cells: rapid responders controlling immunity and disease. *Int J Biochem Cell Biol* 37 (7): 1337–1343
9. MOLLING J W, KOLGEN W, VAN DER VLIET H J, BOOMSMA M F, KRUIZENGA H, SMORENBURG C H, MOLENKAMP B G, LANGENDIJK J A, LEEMANS C R, VON BLOMBERG B M, SCHEPER R J, VAN DEN EERTWEGH A J 2005 Peripheral blood IFN-gamma-secreting Valpha24(+)Vbeta11(+) NKT cell numbers are decreased in cancer patients independent of tumor type or tumor load. *Int J Cancer* 116 (1): 87–93
10. RENUKARADHYA G J, KHAN M A, VIEIRA M, DU W, GERVAY-HAGUE J, BRUTKIEWICZ R R 2008 Type I NKT cells protect (and type II NKT cells suppress) the host's innate antitumor immune response to a B-cell lymphoma. *Blood* 11 (12): 5637–5645
11. CHEN W, FORD M S, YOUNG K J, ZHANG L 2004 The role and mechanisms of double negative regulatory T cells in the suppression of immune responses. *Cell Moll Immunol* 1 (5): 328–35
12. MYERS J S 2008 – Proinflammatory cytokines and sickness behavior: implications for depression and cancer-related symptoms. *Oncol Nurs Forum* 35 (5): 802–7
13. LEE B N, DANTZER R, LANGLEY KE, BENNETT G J, DOUGHERTY P M, DUNN A J, MEYERS C A, MILLER A H, PAYNE R, REUBEN J M, WANG X S, CLEELAND C S 2004 A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation* 11 (5): 279–92
14. STROUSE T B 2007 The relationship between cytokines and pain/depression: a review and current status. *Curr Pain Headache Rep* 11 (2): 98–103
15. EISENSTEIN T K, HILBURGER M E 1998 Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J Neuroimmunol* 83: 36–44
16. RISDAHL J M, KHANNA K V, PETERSON P K, MOLITOR T W J 1998 Opiates and infection. *J Neuroimmunol* 83: 4–18
17. HOLLMAN N W, DURIEUX M E 2000 Local anaesthetics and inflammatory response. *Anesthesiology* 93: 858–75
18. HONG J Y, LIM K T 2008 Effect of preemptive epidural analgesia on cytokine response and postoperative pain in laparoscopic radical hysterectomy for cervical cancer. *Reg Anesth Pain Med* 33 (1): 44–51
19. EXADAKTYLOS A K, BUGGY D J, MORIARTY D C, MASCHA E, SESSLER D I 2006 Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 105(4): 660–664
20. BIKI B, MASCHA E, MORIARTY D C, FITZPATRICK J M, SESSLER D I, BUGGY D J 2008 Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* 109(2): 180–7
21. SACERDOTE P, BIANCHI M, GASPANI L, MANFREDI B, MAUCIONE A, TERNO G, AMMATUNA M, PANERAI A E 2000 The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* 90 (6): 1411–4
22. SACERDOTE P 2006 Opioids and the immune system. *Palliative Medicine* 20(8): 9 – 15