Personalised medicine. Is anaesthesia a concern?

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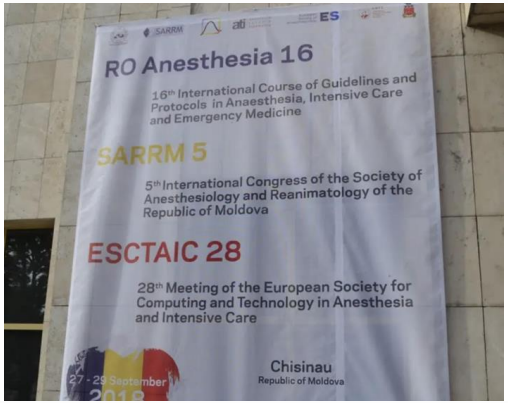
No conflicts of interest



Chisinau, 2018


Dacii Liberi

“Gentlemen! This Is No Humbug”

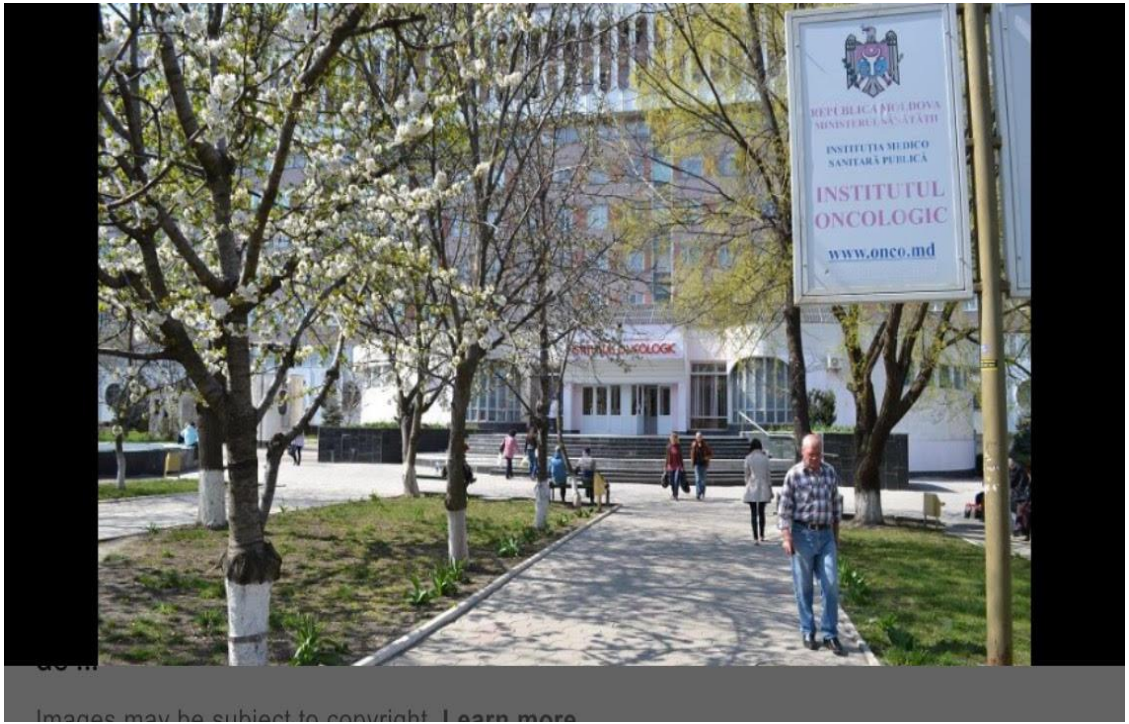
No Humbug!

Areas of involvement of anaesthesia in oncology treatment!

- Surgical interventions - surgical treatment is one of the radical treatment option
- Intensive therapy
- Treatment of acute and chronic pain
- Anesthesia outside the operating room
    - Colorectal screening
    - Diagnostic procedures (template biopsies, bronchoscopy, gastroscopy, colonoscopy)
    - Therapeutic procedures (brachitherapy,)

https://resources.wfsahq.org/atotw/implications-of-anaesthesia-on-cancer-surgery/

Oncologic Institute of Moldova



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Comprehencive cancer Care.

National Program on Cancer Control 2016-2025

29000 admissions in 2022

231000 outpatient visits

Personalized medicine

Uses **genetic biomarkers, imaging techniques, or validated questionnaires**

in order to discriminate between **low- or high-risk** groups and predict which patients are more likely to respond to particular therapies, providing ‘the right therapy, for the right patient, in the right dose, at the right time'uses

The potential clinical **advantages** of a stratified approach are:

- more targeted therapy;
- improved drug efficacy;
- less side-effects;
- and greater certainty of effect in all patient groups.
- Ultimately, knowing which patient characteristics accurately predict outcomes, a shift in medical culture should occur from treatment to prevention

Anaesthesia. Combination of art and science

Does one size fits all?

- Genetic
- Phisiologic factors
- Comorbidities
- Psychologic/social

How might the speciality of anaesthesia adopt stratified medicine.

postoperative pain as an example,

-genetic polimorhysm

Opioid medication - μ-opioid receptor, ATP-binding cassette subfamily B, interleukin-1 receptor antagonist, catechol-*O*-methyltransferase, cytochrome 2D6 enzyme, and melanocortin-1 receptor play a role in patient response to analgesics.

- **Physiologic factors** - depression, anxiety, and catastrophizing; physical tests such as endogenous modulation and suprathreshold temperature;and clinical symptoms such as severe postoperative pain[15] play some part in predicting postoperative pain,

- Examples of drug toxicities that can be predicted by P450 polymorphism include those exerted by codeine, tramadol, NSAIDS, antiemetcs (https://academic.oup.com/toxsci/article/120/1/1/1664504)

https://www.bjanaesthesia.org.uk/article/S0007-0912(17)31665-3/fulltext

NMBA

Decreased plasma cholinesterase activity, whether caused by genetic or non-genetic factors, results in more prolonged durations than seen after suxamethonium

Phenotype	Time to first response to train-of-four stimulation; min	Time to sufficient recovery (train-of-four ratio ≥ 0.9); min
Normal	10–15	25–45
Heterozygous for the usual and at least one of the abnormal genes	15–35	30–60
Homozygous for two abnormal genes	120–480	180–640

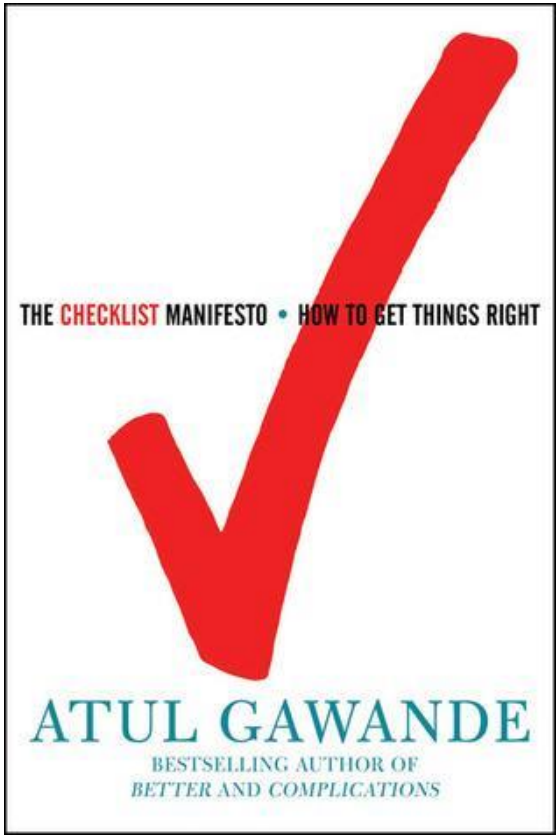
Safety First!

Anesthesia pioneer role in patient safety

First safety program in US, APSF

closed claim study

Anaesthesia mortality rate drop



“There should be no deaths due to anaesthetics”,

Macintosh R: Deaths under anaesthetics. Br J Anaesth 1948; 21: 107–36

DECLARAŢIA DE LA HELSINKI CU PRIVIRE LA SIGURANŢA PACIENTULUI ÎN ANESTEZIOLOGIE

Goal achieved!?

Safer anaesthesia,

vital functions restored

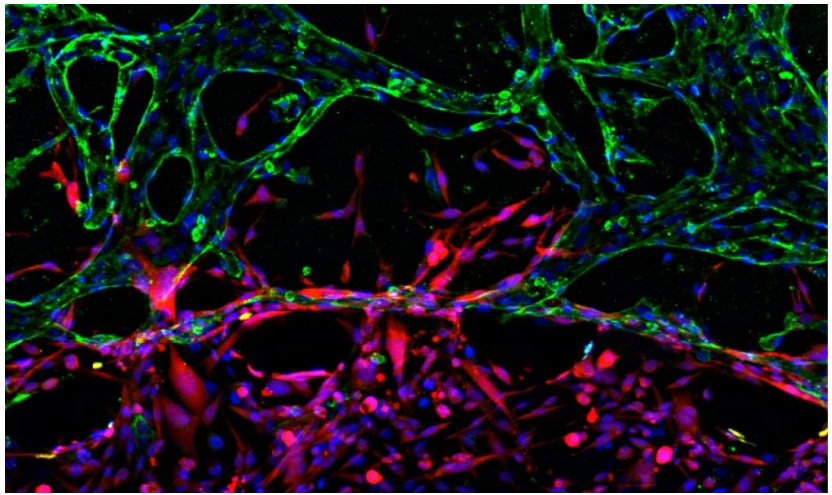
pain control,?

Reduced postop morbidity/mortality

Patient Happy,

surgeon happy!

What about long term effects of anaesthesia on cancer recurrence and metastasis?



To discuss:

- Mechanisms of metastasis;
- Effects of anaesthesia;
- Advantages and disadvantages of different anaesthesia types;
- Drug effects;
- Worldwide research studies.

Mechanisms of metastasis

The surgical procedure, itself, performed for curative purposes is a risk factor for metastasis by creating an environment with high potential for tumour cell survival . Metastasis occurs when cancer cells succeed in suppressing the immune system (decreases the activity of natural kinase cells)

. Virtually, all perioperative antineoplastic treatment creates relative immunosuppression:

•manipulations on the tumor during surgery favor the penetration of its cells into the systemic circulation;

•the presence of the primary tumor is an inhibitor of angiogenesis and its removal eliminates the defense mechanism;

•perioperative immunosuppression, which primarily influences cellular immunity. A negative role is played by neuroendocrine and inflammatory components in response to stress, but also by the action of preparations administered during anesthesia and postoperative analgesia;

• hypothermia can also be attributed to the suppression of immune function.

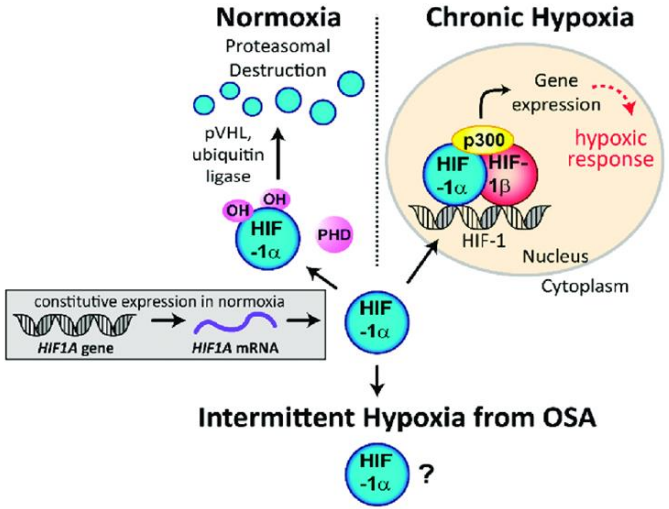
The physiological response to stress in surgery causes relative **immunosuppression** through the release of hormonal mediators: catecholamines, prostaglandins, and growth factors.

Prostaglandins and catecholamines can cause activation of receptors that increase the metastatic capacity of cancer cells (e.g. B2-adrenergic) and cyclooxygenase-2 receptors.

Inflammation associated with tissue trauma results in the release of cytokines (interleukin-6 and prostaglandin E2) that can cause inhibition of natural killer (NK) cell activity. The role of NK cells is essential in the perioperative phase as they are responsible for the detection and destruction of circulating tumour cells.

Another factor contributing to cancer recurrence is tissue **hypoxia**.

This causes an increase in the expression of transcription factor 1-alpha (HIF1A), which plays an important role in promoting cellular pathways for angiogenesis, cell proliferation, and metastasis. The mechanism of action of HIF1A is to determine the expression of vascular endothelial growth factor (VEGF). This, in turn, stimulates tumor growth and angiogenesis, can remodel lymphatic pathways, allowing metastasis of tumor cells.



Haemotransfusion is associated with increased risk of metastasis.

Transfused blood induces immunosuppression. There is scientific evidence of decreased natural killer cells, T-helper cells and decreased cytokine production.
The term immunomodulation induced by haemotransfusion has been proposed since 1973.

It is also associated with increased risk of cancer recurrence in patients given blood components perioperatively.

Perioperative hypothermia is a factor that increases the risk of wound infection. It is considered, that maintaining a normal temperature in a patient during the perioperative period is more effective, than antibiotic prophylaxis. Hypothermia during general anesthesia inhibits cellular immunity, especially of natural killer cells, thus increasing cancer recurrence.
For example, intraoperative decrease of body temperature up to 35.5 ºC, in patients who underwent surgery on the organs of the abdominal cavity, the immunosuppressive effect increases.

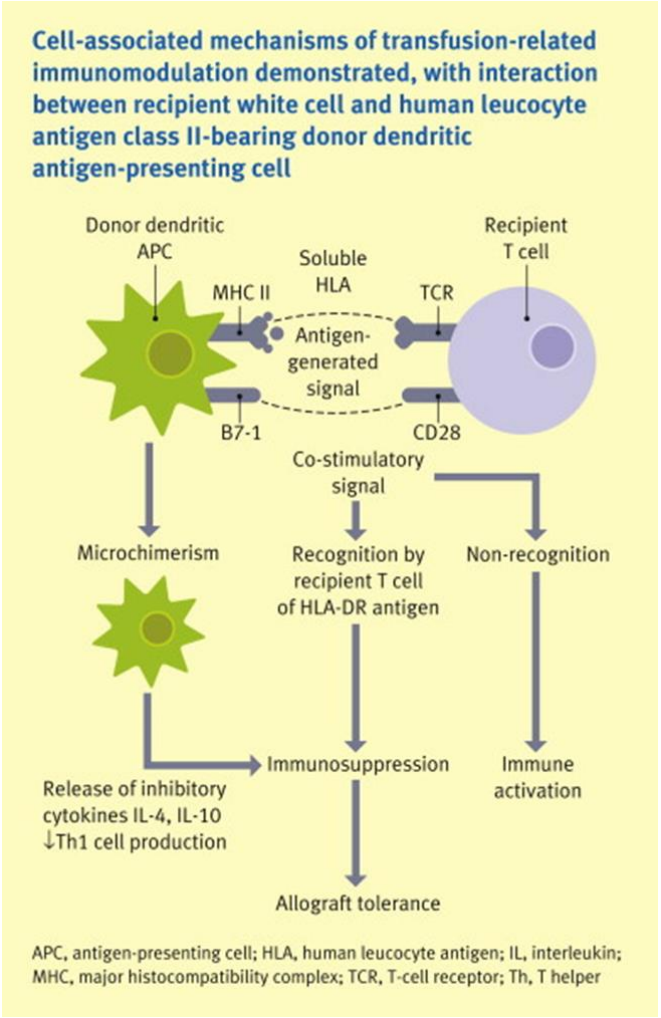


Fig.2 [25]

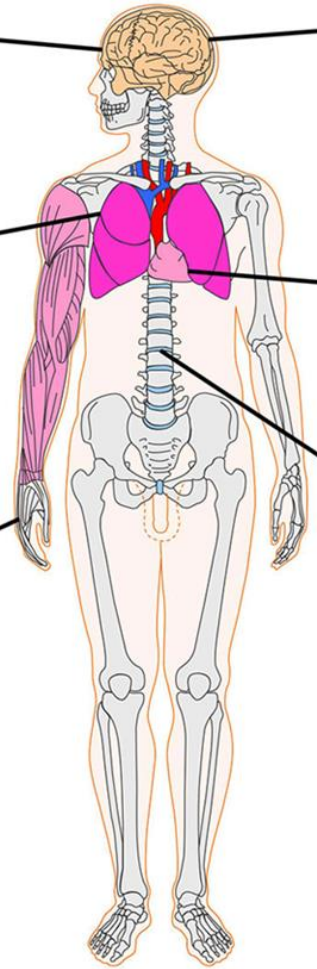
Remedies with suppressive effect on immune system during the perioperative period.

Drug	Potential action on anti-cancer immunity
Ketamine	Decreases the amount and activity of natural kiler cells.
Tiopental	Decreases the amount and activity of natural kiler cells.
Midazolam	Decreases the plasma concentration of IL-8 cytokines. This favors immunosuppression, because IL-8 is a factor that activates neutrophil chemotaxis and adhesion (important components for the normal immune response to surgical aggression)
Inhalatory anaesthetics	In the experiment it inhibits interferon stimulation of natural killer cells. Sevoflurane in vitro decreases the clearance of tumor necrosis factor by natural killer cells. Decreased long-term results in melanoma interventions under inhalation anesthesia compared to regional anesthesia are demonstrated.
Nitrous oxide	In the experiment, it causes the appearance and accelerates the formation of metastases in the lungs and liver. It is the most powerful stimulator of the formation of metastases in the liver among all the anesthetic preparations studied.
Morfine	In the experiment it inhibits cellular immunity and the activity of natural killer cells
Fentanil	Decreases the amount and activity of natural kiler cells in clinic
α2-adrenoreceptor agonists (clonidine)	It accelerates cell proliferation and inhibits apoptosis. In the experiment, it favors the progression of mammary gland tumor growth

Remedies with positive effect on immune system during the perioperative period.

Drug	Potential action on anti-cancer immunity
Propofol	It has an immunoprotective effect, decreases the metastatic potential of a line of cancer cells, induces the process of apoptosis, increases the synthesis of anti-inflammatory cytokines IL-10
Local Anesthetics	Lidocaine inhibits the activity of the receptors of the endothelial growth factor and the proliferation o tumor cells (in vitro). Ropivacain inhibits the growth of tumor cells (in vitro).
Tramadol	In the experiment and in the clinic it stimulates the activity of natural killer cells, it does not allow the metastasis of the tumor which is induced by the surgical intervention (experimental data).
Nonsteroidal anti-inflammatory drugs	In the experiment, the negative action on angiogenesis and tumor growth is demonstrated, induce apoptosis, balance the negative action of morphine on the immune status.
Blockers of β-adrenoreceptors	In the experiment it inhibits tumor growth, which is determined by β-adrenergic stimulation.

Friend or Foe?



TIVA

Basic science and retrospective data mostly suggest benefit, likely friend. RCTs are limited. Three studies discussed in this narrative suggest patient race/ethnicity may be a factor with some risk reduction seen in Asian women with breast cancer. Few studies suggest harm, though cancer type could be a factor.

Volatile anesthesia

Basic science and retrospective data mostly suggest harm to no benefit. Few studies suggest survival benefit through promoting cellular death in some cancer types. RCTs are limited. Three studies discussed in this narrative suggest there is no change in outcome between volatile anesthesia and propofol TIVA.

Intravenous Lidocaine

Friend, *in vitro, in vivo* and retrospective data suggest benefit. RCTs unavailable at this time though ongoing. No studies to suggest harm. Use of intravenous lidocaine infusions have been shown to reduce opioid use and improve postoperative pain scores.

Opioids

Basic science research suggests opioids are powerful immunomodulators that have the potential to increase risk of cancer recurrence. When compared to other multimodal agents opioids show a similar risk profile. Two RCTs discussed in this narrative show conflicting results, one suggesting remifentanil is inferior to paravertebral blocks for decreasing cancer risk.

Dexmedetomidine

Basic science and retrospective data suggest harm and increased risk of cancer recurrence through increased cancer cell survival. RCTs currently not available though are on going. Though no definitive recommendation exists until more is known it would be prudent to avoid using dexmedetomidine for cancer patients undergoing primary resection.

Regional Anesthesia

Inconclusive though likely friend, basic science and retrospective data suggests regional anesthesia is beneficial. However, limited RCT data suggests that there is no benefit over opioid analgesia. No studies have shown significant harm or increased risk of recurrence or metastatic conversion.

EURO-PERISCOPE

The E[illegible] Cancer Research Group (Euro[illegible]

This network emerged from EU-COST Action 15204 (2016-2021) of the same name, EURO-PERISCOPE. This was an EU-funded network of doctors, mainly but not exclusively anaesthesiologists and also surgeons, nurses and scientists, actively engaged in perioperative care of the cancer patient. It was Chaired and instigated by Donal Buggy (Mater University Hospital, Dublin, Ireland). It focused on the research question: *'Can anaesthetic, analgesic or perioperative interventions during tumour resection surgery influence risk of recurrence?"* This collaborative network involved >120 participants in 22 European and near neighbour nations. The activities of the EU COST Action were halted in the final year of its term due to the Coronavirus pandemic. ESAIC Euro-Periscope RG will take over where the EU network ended, at least for the anaesthesiologists and affiliated scientists.

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REVISTA DE ȘTIINȚE ALE SĂNĂTĂȚII DIN MOLDOVA

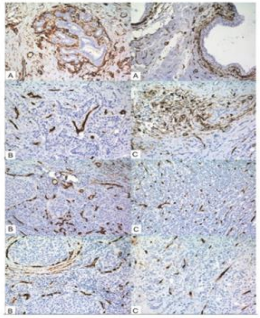
Vol. 10 Issue 1, March 2023

Category B

CONTENT HIGHLIGHTS:

THE INFLUENCE OF DIABETES MELLITUS ON BLOOD VESSELS AMOUNT IN CASE OF BREAST CANCER

Ecaterina Foca, Dumitru Brinza, Elena Portnoi, Ecaterina Carpenco, Valeriu David, Lilian Saptefrati, Veaceslav Fulga



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CONTENT

RESEARCH ARTICLES

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UDC: 616-006.6-009.624

REVIEW ARTICLE

Loco-regional analgesia in oncology. Influence on cancer recurrence rate. Literature review.

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ABSTRACT

Introduction. A major role and, at the same time, a question mark, both for patients and doctors, is the possibility that drugs and anesthetic techniques influence cancer metastasis. Cancer is the leading cause of death worldwide. This trend will continue in the future. Most of the deaths of cancer patients are due to complications arising from metastases. The metastasis process of a tumor depends on its intrinsic properties and interaction with the host. The treatment of tumors by performing a surgical intervention, radical or palliative, has a significant impact. For these reasons, the rate of survival and migration of cancer cells in the perioperative period is studied quite insistently and complexly. Thus, surgical intervention and anesthetic support in cancer patients becomes of great importance, because it represents the vulnerable link, both from the point of view of the operation itself, as well as the possibility that drugs, anesthetic techniques may or may not influence tumor metastasis.

Material and methods. Primary scientific studies published from 1996 to 2021 dedicated to loco-regional anesthesia and its influence on the perioperative period and on cancer metastasis were studied. To achieve the proposed goal, scientific sources PubMed, Medscape, SCOPUS, MEDLINE were researched. Keywords used for searching: loco-regional anesthesia, fascia plane anesthesia, metastasis. More than 80 reference sources were identified, 67 were selected for analysis.

Results and discussions. The surgical procedure, itself, performed for curative purposes, also known as tumor resection – is a risk factor for metastasis by creating an environment with high potential for tumor cell survival. This stimulates tumor growth and angiogenesis, can remodel lymphatic pathways, allowing metastasis of tumor cells. Hemotransfusion is associated with increased risk of metastasis. Regional anesthesia could reduce cancer recurrence through several mechanisms.

Conclusions. Regional anesthesia could reduce cancer recurrence by reducing the need for opioids or inhaled anesthetics, or by reducing the stress response during surgery. There is scientific *in vitro* evidence of a protective effect of systemic lidocaine on recurrent cancer, although relevant clinical data are limited.

Keywords: cancer recurrence, general anesthesia, regional anesthesia, stress response, opioid analgesics, angiogenesis inducing agents, morphine, onco-anesthesia.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript
The article is a literature review of recent medical publications describing loco-regional anesthesia in oncology and its role in cancer recurrence. Thus, specialists from the Republic of Moldova will have a synthesis of modern research in the field.
The research hypothesis
Local anesthesia/analgesia positively influences patients with cancer and does not contribute to development of metastasis or lead to cancer recurrence.
The novelty added by manuscript to the already published scientific literature
Fascial plane anesthesia/analgesia in oncology is a link of multimodal analgesia and does not influence metastases occurrence. This is a proven, safe and effective method of relieving perioperative pain syndrome in oncology patients.

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Introduction

A major role and at the same time a question mark, both for patients and doctors, is the possibility that drugs and anesthetic/analgesic techniques influence cancer metastasis. Cancer is the leading cause of death worldwide. This trend will continue in the future [1, 2]. Most of the deaths of cancer patients are due to complications arising from metastases. These may result from direct, lymphatic or hematogenous spread. The metastasis process of a tumor depends on its intrinsic properties and interaction with the host [3]. The treatment of tumors by performing a surgical intervention, radical or palliative, have a significant impact [4]. For these reasons, the rate of survival and migration of cancer cells in the perioperative period is studied quite insistently and complexly [5]. Thus, surgical intervention and anesthetic

- the presence of the primary tumor is an inhibitor of angiogenesis and its removal eliminates the defense mechanism;
- perioperative immunosuppression, which primarily influences cellular immunity. A negative role is played by neuroendocrine and inflammatory components in response to stress, but also by the action of preparations administered during anesthesia and postoperative analgesia;
- hypothermia can also be attributed to the suppression of immune function.

The physiological response to stress in surgery causes relative immunosuppression through the release of hormonal mediators: catecholamines, prostaglandins, and growth factors [11]. Prostaglandins and catecholamines can cause

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