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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 can-

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cer 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.

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 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 [6, 7].

Material and methods

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

Results and discussions

After analyses of the sources, we can describe some of the principal mechanisms of metastasis that occur during the perioperative period. The surgical procedure, itself, performed for tumor resection – is a risk factor for metastasis by creating an environment with high potential for tumor cell survival [8]. Metastasis occurs when cancer cells succeed in suppressing the immune system (decreases the activity of natural kinase cells) [9]. Virtually, all perioperative antineoplastic treatment creates relative immunosuppression [10]:

- 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 [11]. Prostaglandins and catecholamines can cause activation of receptors that increase the metastatic capacity of cancer cells (e.g., β2-adrenergic) [12] and cyclooxygenase-2 receptors [13]. 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 [14]. The role of NK cells is essential in the perioperative phase as they are responsible for the detection and destruction of circulating tumor cells [15].

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 [16]. The mechanism of action of HIF1A is to determine the expression of vascular endothelial growth factor (VEGF) [17]. This, in turn, stimulates tumor growth and angiogenesis, which can remodel lymphatic pathways, allowing metastasis of tumor cells [18, 19].

Hemotransfusion is associated with increased risk of metastasis [20]. Transfused blood induces immunosuppression. There are scientific data that show decreased natural killer cells, T-helper cells, and likewise decreased cytokine production [21]. The term immunomodulation induced by hemotransfusion was introduced in 1973. It is also associated with increased risk of cancer recurrence in patients given blood components preoperatively [22]. Hemotransfusion is associated with increased risk of metastasis [20]. Transfused blood induces immunosuppression. There is scientific evidence of decreased natural killer cells, T-helper cells and decreased cytokine production [21]. The term

immunomodulation induced by hemotransfusion has been proposed in 1973. This is also associated with increased risk of cancer recurrence in patients who are transfused blood components perioperatively [22]. 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 activity of natural killer cells, thus increasing cancer recurrence [23]. For example, intraoperative decrease of body temperature down to 35.5 ºC, in patients who underwent abdominal surgery, has a the immunosuppressive effect[24].

Effects of anesthesia

Clinical trials on the effects of anesthetics on cancer are complicated to conduct because patients need a combination of anesthetic agents. It would be medically and ethically difficult to perform surgery without perioperative pain relief e.g., using only regional anesthesia. Usually, intraoperative analgesia includes both regional analgesic and general anesthetic components. In the following paragraphs, we describe some comparative studies between local and general anesthesia on cancer metastasis. These have been performed on patients with tumors form different location who underwent surgery.

The first large randomized trial in this field for breast cancer surgery and was published in 2019 on approximately 2100 patients who underwent mastectomy or local surgery with axillary dissection, and were randomly assigned to receive regional anesthesia/analgesia (paravertebral block combined with sedation) or general anesthesia (inhalation, opioid analgesia) [25]. Cancer recurrences were similar in both groups: general/combined anesthesia occurring in 10% of patients in each group during a 36-month follow-up. Another study that included more than 1,700 patients who underwent major abdominal or thoracic surgery and were similarly randomized: epidural + general anesthesia versus general anesthesia + postoperative opioids. Thus, overall survival and recurrence-free survival were similar in the two groups at more than five years of follow-up [26]. In a randomized trial including 400 patients with lung cancer who underwent video-assisted thoracoscopic surgery, we have the following results: relapse-free survival and overall survival were similar in both patients receiving general anesthesia + postoperative opioid analgesia and those receiving general anesthesia + postoperative epidural analgesia [27]. In the next paragraphs, we will show the results from other scientific publications in which research has been described regarding the role of anesthetics in the development of metastases according to their mode of action.

General anesthesia (inhalation)

Laboratory studies have suggested some possible mechanism by which inhalational anesthetics may promote metastasis [28-31]. Inhalational anesthetic agents (e.g., isoflurane, sevoflurane, desflurane, and halothane) also have pro-inflammatory effects [32].

General (intravenous) anesthesia

According to multiple researchers that studied the effects of anesthetics on natural killer (NK) cell activity and metastasis development in rats modelled with breast cancer, propofol did not suppress NK cell activity nor did metastases develop, while halothane, ketamine and thiopental both decreased NK cell activity and metastases developed [33].

Regional anesthesia/analgesia

Regional anestheisa/analgesia could reduce cancer recurrence through several mechanisms, for example:

- decreasing the stress response to surgery (by pain control or sympathetic blockade) [34, 35];
- reducing the need for opioids or inhalants;
- via direct effects related to absorption of local anesthetics.

This type of anesthesia/analgesia is the most intensely discussed by the medical community because of the prospects for their use in general surgery as well as in oncology. Thus, we will point to studies that have been performed on large groups of patients.

The first large international randomized trials were conducted comparing regional anesthesia + propofol and general anesthesia with sevoflurane + opioids. It found similar relapse rates after surgery for breast cancer [25]. The same results were obtainted in two other studies describing epidural versus intravenous general anesthesia + opioids [26, 27]. In 2014, more than 3,000 people were included in studies and underwent cancer surgery. According to these data, no difference in cancer recurrence or overall survival was observed in patients given general anesthesia + epidural and general anesthesia alone [36]. Subsequently in 2017 were conducted 28 studies (retrospective, observational and randomized) including more than 67,000 patients who underwent surgery for multiple cancers. Overall and relapse-free survival was the same in those who received regional anesthesia with or without general anesthesia [37]. Ten other retrospective studies including approximately 13,760 individuals, after radical prostatectomy, with a diagnosis of prostate cancer were also reviewed. According to the results of these studies, regional anesthesia with or without general anesthesia, was described with better overall survival, but similar cancer recurrences with general anesthesia alone [38]. In conjunction with follow-up studies, investigations of the immune status of breast cancer patients treated with surgery given propofol + paravertebral regional anesthesia and inhaled general anesthesia + opioids was performed. Thus, it has been shown that in patients receiving regional and intravenous anesthesia in breast cancer tissue there is both increased infiltration with immune cells, increased apoptosis of cancer cells and maintenance of NK cell cytotoxicity [29, 30, 39].

Amide local anesthetics, particularly lidocaine, have been used for a long time in pain management during general anesthesia, as well as systemic intravenous infusions, in neuraxial and peripheral nerve blocks. Lidocaine is a

short-acting substance with minimal toxicity. It blocks voltage-dependent sodium channels, which are responsible for the generation of impulses in sensory nerve endings and conduction of pain impulses through nerve fibers. [40-42] Along with its analgesic effect, lidocaine also exhibits antioncogenic and anti-inflammatory properties through various pathways [43-47]. In general, local anesthetics, according to some studies, have antitumor and antimetastatic properties. These effects are achieved through several mechanisms, such as:

(1) direct cytotoxicity, induction of apoptosis;
(2) inhibition of proliferation, migration and invasion;
(3) modulation of gene expression through methylation [48].

Local anesthetics (LA) in high concentrations are known to be cytotoxic to neuronal cells. This seems to be correlated with the lipid solubility of LA. As a result, this process includes cell death by necrosis or apoptosis. All local anesthetics cause necrosis, and lidocaine and bupivacaine cause apoptosis in neuroblastoma cells [49, 50] as well as in breast and thyroid cancer cells [51, 52]. Apoptosis is controlled by an intracellular cysteine group – caspases. Chang and colleagues demonstrated that treatment of breast cancer cells with clinically relevant concentrations of lidocaine and bupivacaine induced caspase formation [51]. As a result, cell viability decreased and the process of apoptosis was triggered [53, 54]. Another article studied the action of lidocaine and bupivacaine on thyroid cancer cells, the latter induced apoptosis. This effect was mediated via the protein kinase pathway [51]. Local anesthetics also inhibit proliferation, migration and invasion of cancer cells. Yoon and colleagues introduced tetracaine and lidocaine into the tumor region. This has been shown to inhibit microtubule expansion and the ability of tumor cells to promote aggregation and reattachment [55]. LAs may also influence proliferation and invasion through their effects on cell signaling pathways [56, 57].

Several studies have been carried out on this issue:

- Mammamoto demonstrated that lidocaine, in clinically relevant concentrations, decreased the invasiveness of HT1080 cells by inhibiting HB-EGF excretion [58];
- Sakaguchi showed that lidocaine inhibited EGF-induced proliferation of tongue cancer cells [59];
- Piegeler demonstrated that amide local anesthetics reduced TNF-α-induced Src activation and ICAM-1 phosphorylation in human lung cancer cells and inhibited cancer cells [60];
- Baptista-Hon and colleagues demonstrated that ropivacaine inhibiting sodium channels decreases cell invasion. This is due to direct effects on cancer cells [61], but also indirect effects by blocking noxious stimuli [62].

Local anesthetics also inhibit cancer cell proliferation by modulating gene expression through DNA methylation. Lidocaine has been shown to demethylate DNA in breast cancer cells [63].

Since, cancer treatment is mainly surgical, used anesthesia must also be appropriate, meeting certain criteria. In general, this needs to be effective, safe and with as lowest risk of early and late postoperative complications as possible. To achieve this goal, the anesthesiologist has several methods in his arsenal: strong general anesthetics, effective analgesics both opioid and non-opioid, different types of loco-regional anesthesia/analgesia. Thus, nowadays, the radical method of treatment in oncology is considered surgery. However, its late results are insufficient, because the percentage of tumor recurrence is considerable. Cancer metastases are the cause of death in 90% of cases [64]. It is necessary for anesthetists working in cancer centers to differentiate between anesthesia/analgesia methods and their effects on cancer recurrence. Thus, research conducted by Ovechkin A. M. in 2012 at the First Moscow State Medical University *I. M. Sechenov*, showed us in major lines the anesthetic/analgesic remedies that influence the immune status of the oncological patient (Table 1, 2) [65].

Table 1. Remedies with suppressive effect on immune system during the perioperative period [65].

Drug	Potential action on anti-cancer immunity
Ketamine	Decreases the amount and activity of natural killer cells.
Thiopental	Decreases the amount and activity of natural killer 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).
Inhalation anesthetics	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 experiments, 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
Morphine	In the experiment it inhibits cellular immunity and the activity of natural killer cells
Fentanyl	Decreases the amount and activity of natural killer 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

Note: IL-8 - Interleukin 8.

Table 2. Remedies with positive effect on immune system during the perioperative period. [65]

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 of 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

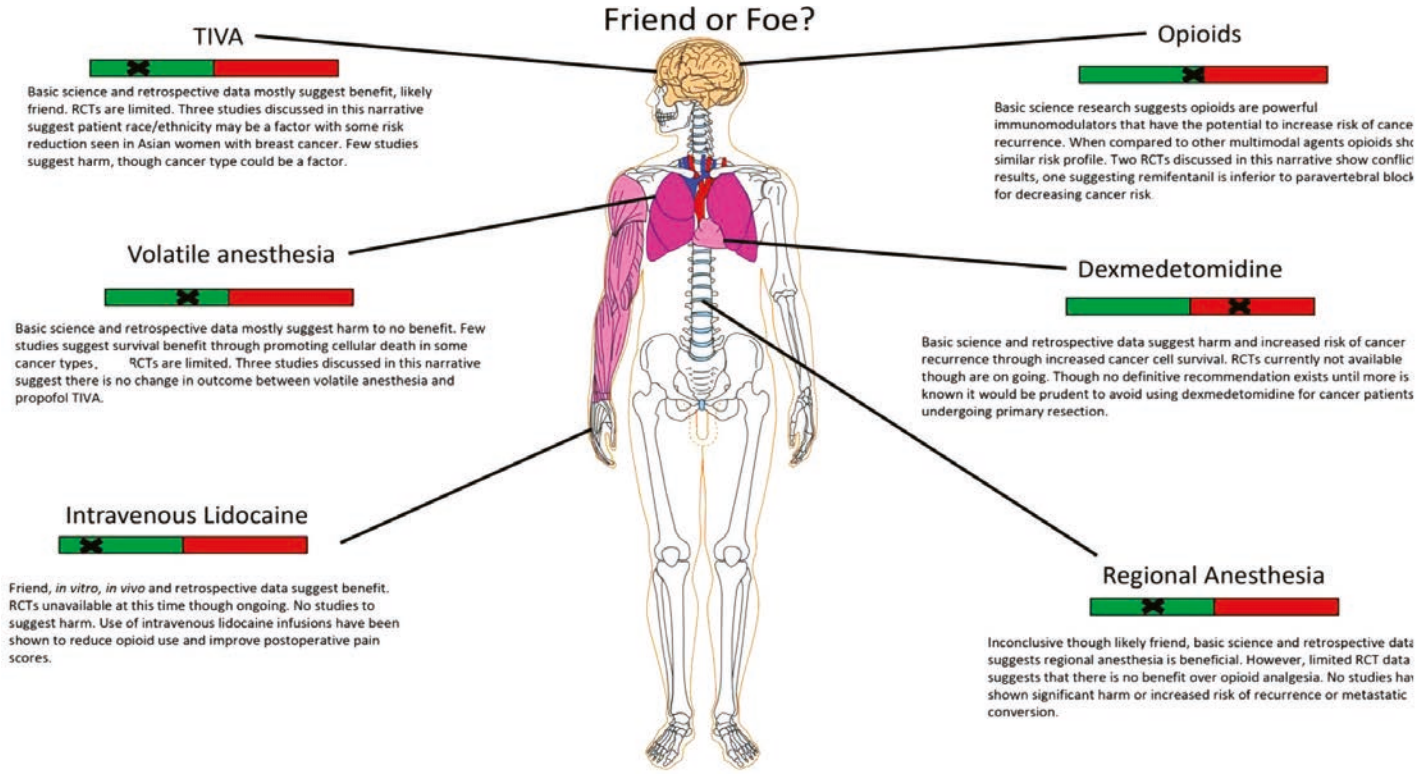

Fig. 1 Anesthesia and Cancer, Friend or Foe?

Julio Montejano and Vesna Jevtovic-Todorovic in 2021 wrote an article: *Anesthesia and cancer, Friend or foe? A narrative analysis.* In the article, they exemplified the types of anesthesia and their interaction with cancer (Fig. 1) [66].

Conclusions

Surgical treatment in cancer patients is associated with a multitude of factors that directly or indirectly may influence tumor cell survival, inflammatory and stress responses to surgical aggression. Inhalational anesthetics have pro-inflammatory effects and may influence cancer cell survival, including immune suppression and up-regulation of hypoxia-inducible factors (HIF1A). However, experiments on animal and human regarding cancer recurrence after the use of inhalational agents were conflicting. Propofol has anti-inflammatory and antioxidant effects that protect against immune suppression and may preserve natural killer (NK) cell activity. Clinical trials comparing intravenous and inhaled anesthetic agents have shown mixed results in terms of cancer recurrence. Regional anesthesia could decrease cancer recurrence by reducing the need for opioids or inhaled anesthetics, or by reducing the stress response during surgery. Other studies suggest that opioids might influence metastasis or tumor growth, however, the evidence is conflicting and inconclusive. There is *in vitro* scientific evidence of a protective effect of systemic lidocaine on recurrent cancer, although relevant clinical data are limited.

Conflict of interest

The authors declare no conflict of interest, financial and non-financial, associated with the subject of this paper.

Authors' contribution

All authors contributed equally to the drafting and writing of the manuscript. The authors read and approved the final version of the manuscript.

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