

Effects of the Type of Anesthesia (Inhalation or Intravenous) for Survival or Recurrence After a Cancer Surgery

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Received:  January 27, 2020

Published:  February 03, 2020

Frozen Shoulder

Surgery has a very important role in solid tumors multimodal treatment. The primary excision can be curative itself or can be combined with neoadjuvant or adjuvant chemotherapy and / or radiotherapy. Despite therapy advances, recurrence and metastases appear as an important source of morbidity and mortality in cancer patients. There is a huge growing interest in events related to surgery and the perioperative period that not only help to release cancer cells into general circulation, but also facilitate its growing, leading to regional recurrences and metastases. Data obtained from laboratory and animal experimentation suggest that anesthetics drugs may affect long-term results after cancer surgery. In this

review, we summarize the experimental and clinical data that we have nowadays, and we present the potential role of anesthetic techniques (inhalation and intravenous) in cancer recurrence and survival.

Materials and Methods

A bibliographic search has been done out using Medline / PubMed database and Embase, using as key words “anesthesia and metastasis”, “anesthetic drugs and cancer”, “halogenated and cancer”, “volatile anesthetic agents and cancer”, “propofol and cancer”, anesthetic technique and cancer”. They have been included the most relevant English or Spanish papers (Table 1).

Table 1: Surgery immune effects that would predispose to tumor released into bloodstream.

Surgery Factors Which Inhibit Immune Response
Cellular immune function inhibition due to neuroendocrine stress response induced by surgery
Tumor cell migration due to surgical manipulation
The humoral Factors Reduction
i. The antiangiogenic protective factors (angiostatin, endostatin) reduction
ii. The angiogenic factors (vascular endothelial growth factor or VEGF) increasing
The growth factors role: transforming growth factor beta (TGF-β), with cell proliferation and tumor vascularization functions (3)
i. Transfusion
ii. Hypothermia
iii. Pain
Anesthetic Drugs:
i. Volatile anesthetics
ii. High dose opioids
iii. Nitrous oxide
iv. Ketamine
v. Pentotal

Results

Experimental Evidence

- a. Surgery itself and the neuroendocrine response related to stress have a negative effect on immune system due to cell-mediated immunity depression they cause. Even after the complete tumor excision, circulating tumor cells released during the surgical procedure may lead to recurrence or metastasis thanks to their ability to avoid immunological process [1]. Thereby, they can decrease antiangiogenic protective factors concentration (e.g. angiostatin and endostatin) while increase angiogenic factors such as vascular endothelial growth factor (VEGF). Surgery is also associated with transforming growth factor-beta (TGF- β) which plays a significant role in tumor blood supply and cell proliferation [2].
- b. Anesthesia process also interacts with several immune functions, including those related to neutrophils, macrophages, dendritic cells, T cells and natural killer cells (NK). In vitro studies about the possible metastasis induction of inhalation anesthetics role are based on their time-and-dose-dependent inhibitory effects. Thus, they modify neutrophil function, suppress mononuclear cells cytokines release, decrease lymphocyte proliferation and promote lymphocyte apoptosis. Moreover, inhalation anesthetics also promote the growth and proliferation of endothelial stem cells (proangiogenic effect) which would improve tumor growth and / or teratogenicity [3]. Nevertheless, propofol does not seem to depress immune system, according to evidence available. It seems to improve NK cells cytotoxicity, to reduce motility and tumor cells invasion, to inhibit cyclooxygenase and to not promote HIF (antiangiogenic effect) synthesis [4].
- c. Opioid drugs inhibit both cellular and humoral human immune function, increase angiogenesis and promote the

growth of breast tumoral cellular in rodents. In this way, they also interfere with immune functions by depressing NK cells activity [3] However, these drugs can reduce stress response caused by pain and offer some benefit. Clinical evidence.

d. Most of the available evidence nowadays is based on intermediate results (substituted variables: cell reduction, inhibitory activity...) such as the previous ones mentioned and the only studies with patient-centered results (final variables: survival, mortality, recurrence) are the ones that we are going to review. A recent retrospective analysis composed by more than 7,000 patients from an oncology hospital in United Kingdom was carried out to determine long-term survival of patients who were receiving inhalation anesthesia (isofluran or sevoflurane) versus intravenous anesthesia (propofol and remifentanyl) in cancer surgery. After several analysis, including multivariate analysis, it was found that those who received inhalation anesthetics were those who had a lower survival (HR [hazard ratio] 1.46; 95% CI 1.29-1.66 if we compared with the group who received intravenous anesthesia [5].

e. Lee JH, the author of another retrospective analysis composed by more than 300 patients taken from an oncology hospital South Korea, determined the association between the type of anesthesia (inhalation or intravenous) and recurrence or survival in patients that have undergone radical mastectomy. Large significant differences were not found between the two groups about survival (HR of 0.550; 95% CI 0.311-0.973) but they found a lower recurrence in the intravenous anesthesia group Enlund M [6] found greater survival in patients undergoing cancer surgery with propofol compared to sevofluran, but when multivariate analysis is used with variables such as type of tumor (breast, colon and rectum), this association disappears [7] (Table 2).

Table 2: Efectos de los agentes anestésicos sobre la inmunidad contra el cáncer.

	Positive Implications	Negative Implications
Ketamine		NK cell suppression activity and increase of viable cancer cells in lung cancer
Thiopental		Similar effects to ketamine
Opioids Inhibitors	Pain control	Proangiogenic
	Immune stimulate caused by its interaction with μ receptor	Dose-dependent cellular and humoral immunosuppression (morphine)
	Synthetic opioids (fentanyl y remifentanyl) used in low doses don't disturb immune process	Reversible by naloxone (8)
		Prevention with Cox-2 inhibitors (9)
NSAIDs	Anti-tumoral and anti-angiogenic properties (especially in preoperative)	Immunosuppression
COX2 Inhibitors (COXIBs)	Similar effects to NSAID	
	Interferon release Y	
Nitrous oxide	No recurrence	Cellular immunosuppression (neutrophils, NK cells and lymphocytes) and humoral immunosuppression (increased factors induced by hypoxia)
Volatile Anesthetics		
Propofol	Activation and differentiation of helper T lymphocytes. COX-2 inhibitory activity (10); interferon release Y Greater attenuation of inflammatory response due to stress	

Discussion

Unfortunately, there is a drawback to available evidence; in vitro conditions used in many studies do not accurately replicate cancer cells biological condition. Therefore, the speculative extrapolation of these results to clinical scenario is not ideal. However, retrospective clinical studies about the type of anesthesia (inhalation versus intravenous) and cancer recurrence or survival after tumor excision are beginning to be published. The main disadvantages of these retrospective studies are selection, information and confusion biases. Wigmore [5], incorporated the propensity analysis, which is the best method to control known confounding variables in observational studies. However important variables such as type (including more than 20 cancer types with different prognoses), cancer stage or mortality attributable to cancer (despite it had been considered total mortality) was not considered. Notwithstanding that, the strength of this study falls on the large number of patients included. However, Lee JH [6] included in his study a single type and stage of cancer at the beginning of the study, but it still seemed that there were biases not included in the analysis, such as the use of nitrous oxide or morphics and the anesthetic technique preference of anesthesiologists. Moreover, they could also exist several hidden confounding factors which were not taken into account in a multivariate analysis of retrospective, observational, non-randomized data. About these words, it is also important to consider the regional anesthetic techniques (RA), which are almost always a complement to general anesthesia. Studies have demonstrated lots of advantages of RA in cancer patients by reducing recurrences. The role of intrathecal and epidural opioids commonly used in regional analgesia and pain management has not been explored [8].

As mentioned previously, immune function combined with surgical stress and the direct effects of anesthetic drugs, create a favorable environment for tumor growth and dissemination, which

finally affect patient survival. Reducing the response to surgical stress, minimizing inflammation and using optimal anesthetic and analgesic techniques are the main key to reduce long-term negative effects of cancer surgery. However, overall progress in this area, the actual lack of evidence leads to the impossibility of change our daily clinical practice. More and better randomized clinical trials, prospective cohorts are needed to prove that there is causality between the type of anesthesia and cancer recurrence.

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DOI: [10.32474/GJAPM.2020.02.000145](https://doi.org/10.32474/GJAPM.2020.02.000145)



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