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REVIEW

Opioids and cancer recurrence: a brief review of the literature

Juan P. Cata[1,2,4], Dario Bugada[3,4], Maurizio Marchesini[4,5], Manuela De Gregori [4,6], Massimo Allegri[3,4]

[1]*Department of Anesthesiology and Perioperative Medicine, MD Anderson Cancer Center, Houston, Texas, 77030, USA*
[2]*Anesthesiology and Surgical Oncology Research Group, Houston, Texas, 77401, USA*
[3]*Department of Surgical Sciences, University of Parma, Parma, 43100, Italy*
[4]*SIMPAR Group, Parma, 43100, Italy*
[5]*Anesthesia Intensive Care and Pain Service Azienda Ospedaliera Universitaria Parma, 43100, Italy*
[6]*Pain Therapy Service Foundation IRCCS Policlinico San Matteo, Pavia, 27100, Italy*

Correspondence: Juan P. Cata
E-mail: jcata@mdanderson.org
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Opioids are the most commonly used analgesics during and after cancer surgery and in patients with advanced malignancies who suffer from moderate to severe pain. It has been suggested that opioids can promote cancer progression through different mechanisms including a direct effect on malignant cells, stimulation of angiogenesis and immunosuppression. In contrast, other studies have shown that opioids have anticancer effects. The results of clinical studies remain controversial with some evidence indicating that a high expression of the mu opioid receptor is an independent factor of tumor progression while other studies indicate that the administration of opioids perioperatively is associated with cancer recurrence. Unfortunately, all those clinical studies are retrospective and suffer from significant confounding variables and biases. To date, there is no solid evidence to suggest the avoidance of opioids in cancer patients with moderate to significant with the goal of reducing cancer recurrence. Some authors have suggested the use of spinal administration of opioids in order to reduce systemic effects. Careful use of opioids should be advise to reduce side effects or hyperalgesia in relation to specific needs of the patients.

Keywords: Opioids; cancer cells; microenvironment; cancer recurrence

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Introduction

Surgery represents the treatment of choice for the five most common cancers in adult patients and is indicated in more than two-third of patients with early non-small cell lung cancer (NSCLC) and breast cancer.[1] Therefore, it is expected that the number of patients who will undergo surgery worldwide to diagnose, stage, or treat their cancer will continue to increase in the recent future. Opioids are the most commonly prescribed analgesics in the perioperative period of cancer surgery, but despite of being effective analgesics their use is associated with a variety of adverse events [2]. Opioids are also often used in oncological patients with moderate-to-severe pain secondary to metastatic disease or complications related to chemotherapy or radiation [3-5]. Over the last decade, several investigations have pointed towards a potential negative impact of opioids in patients

Table 1. The effect of opioids on malignancies under different experimental conditions

Type of cancer	Type of study		
	In vitro	In vivo animal	Clinical
Lung adenocarcinoma	Increase in proliferation and invasion. Stimulation of EMT transformation	Tumor growth increase after short-term exposure but decrease after long-term treatment	Decrease in RFS and OS in patients undergoing surgery and those with metastatic disease
Breast cancer	Pro- and antitumoral effects	Mixed findings	Mixed findings
Prostate cancer	Antiproliferative effects in some cell lines	No studies available	Mixed findings
Gastrointestinal cancer	Predominant antiproliferative effects in oesophageal and gastric cells. No effect on liver and pancreatic cell lines.	Inhibition of tumor growth in gastric cancer mouse model.	Mixed findings
Ovarian cancer	No effect on cell proliferation	No studies available	Association between the use of regional intraoperative anaesthesia and low opioid consumption, and longer PFS
Glioblastoma	Antiproliferative effects	Inhibition of tumor growth	No studies available

RFS: recurrence free survival, PFS: progression free survival.

undergoing cancer surgery and in those with advanced malignancies [6-8]. Specifically, it has been suggested that the use opioids could be responsible for short- and long-term postoperative adverse events including immunosuppression and cancer recurrence [6, 9].

Mu opioid receptors (MORs) are expressed in cancer cells such as lung adenocarcinoma, gastric carcinoma cells and ER-positive breast cancer cells in which they can modulate the ability to proliferate, migrate and invade depending on the type of opioids, dose and duration of exposure [10-12]. MORs are also present in cells that are part of the tumor microeviroment. Specifically, MORs are expressed in macrophages, neutrophils and lymphocytes in which they can also alter their function, phenotype and the release of soluble factors such as cytokines and chemokines. For instance, macrophages change their phenotype from M1 (antitumoral) to M2 (protumoral) after being exposed to opioids [13].

The present review manuscript summarizes the current literature regarding the effects of opioids on cancer cells and the microenvironment, and the clinical studies that have investigated the effects of opioids on cancer recurrence.

Opioids receptors, exogenous opioids and cancer cells

MOR is the site of action of the endogenous peptides enkephalins, β-endorphin, dynorphin A, nociceptins and, agonists such as morphine, fentanyl congeners, methadone and meperidine. The human MOR gene (OPRM1) spans over 200 Kb and consists of 11 exons that combine to yield 17 splice variants [14, 15]. Over 700 SNPs have been described in the gene with variations that differ between races and ethnicities [15]. Furthermore, it has been suggested that the genotypic analysis of *OPRM1* could contribute to investigate the interindividual variability of opioid response and possibly guide treatment in patients with cancer [16-18].

The MOR belongs to the seven-transmembrane receptor superfamily and is coupled with Gi/o proteins [19]. After binding of opioid agonists to the receptor, the release of the inhibitory G_i protein causes inhibition of adenylatecyclase that leads to a reduction in cyclic 3′, 5′ adenosine monophosphate (cAMP) and a decrease in protein kinase A activation [20]. MORs also modulate the activity of the G_0 protein that, in turn, is responsible of the known effects of opioids on ion channels such as Ca^{2+} (inhibition) and K^+ (activation) channels [19].

The direct effect of opioids in cancer cells is complex and not fully understood (Table 1). Activation of MOR has shown to regulate important signalling pathways that modulate proliferation, migration and invasion in several cancer cell lines but with controversial findings. Some in vitro studies indicate that morphine can not only induce cleavage of the DNA in human lung cancer cells but also stimulate phosphorylation/activation of Src, Gab-1, PI3 kinase, Akt and STAT3 via the interaction with the epidermal growth factor receptor (EGFR) [11, 21-23]. All these intracellular changes subsequently induce cell proliferation and invasion, and epithelial-mesenchymal transformation in NSCLC [11, 21]. More importantly, the use of a MOR antagonist can reverse the protumoral effects of opioids [21]. In vivo experiments appear to confirm the protumoral results observed in vitro, i.e. the overexpression of MOR increases tumor growth rates in a xenografts mouse model of human NSCLC [11]. On the contrary, continuous (long-term) administration of morphine appears to reduce tumor growth via inhibition of the hypoxia-induced nuclear translocation of hypoxia-inducible transcription factor 1 alpha and mitogen-activated protein kinases [24]. Maneckjee *et al.* have found that opioids induce apoptosis in lung cancer cells via interaction with nicotinic receptors [23].

Similar dual (pro and antitumoral) effects of opioids have been demonstrated in breast cancer cell lines. Ecimovic *et al.* demonstrated that morphine stimulates cell migration and

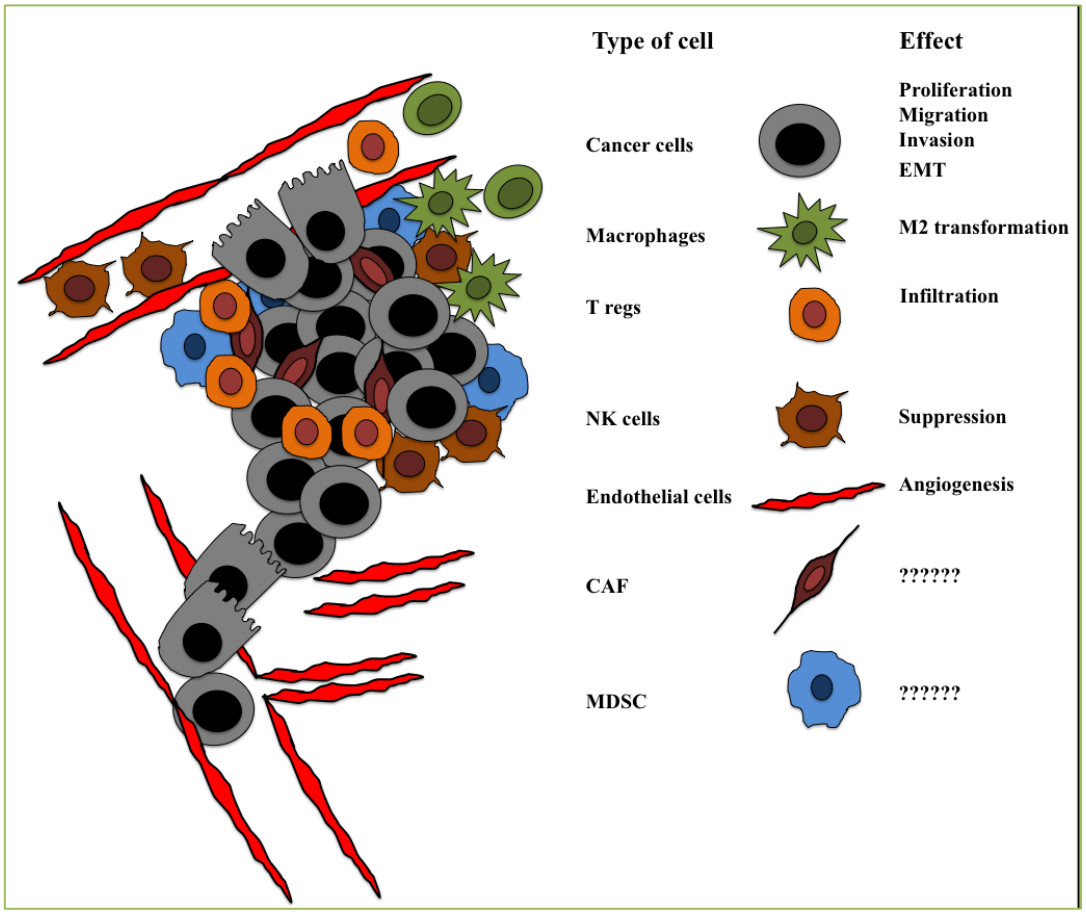

Figure 1. Proposed protumoral effects of opioids. The figure shows the different levels at which opioids can modulate the tumor microenvironment. T regs: T regulatory cells; NK: Natural killer; CAF: cancer associated fibroblasts; MDSC: myeloid derived suppressor cells; ?????: Unknown effect; EMT: endothelial-mesenchymal transformation.

proliferation in ER positive and negative breast cancer cells via an increase in the expression of the NET1 gene [25]. On the contrary, other authors have demonstrated that morphine has dose-dependent anti-proliferative effects, at clinically relevant doses, and induce necrosis, at toxic concentrations, in MCF7 and T47D breast cancer cells [26]. Although, these anti-proliferative effects can be independent on the binding of morphine to MOR and perhaps due to cytoskeleton remodeling via PI3K phosphorylation, recent evidence indicates that activation of MOR increases the expression of PTEN/p53 via PI3k/Akt signaling pathway in MCF7, T47D and MDA-MB231 [27-30]. In vivo studies in animal models of breast cancer have also shown controversial findings. It was initially demonstrated that the administration of fentanyl increased tumor metastasis in rodents inoculated with MADB106 cells but a more recent study in a mouse model for metastatic invasive and $HER2^+$ breast cancer showed that the use of analgesic doses of morphine did not have an impact on tumor growth [31-33]. In remark contrast, opioid agonists such as endopmorphine-1, endomorphine-2 and morphine showed no effect on 2 different ovarian cancer cell lines (OVCAR-3 and SKOV-3) [34].

MORs are also expressed in glioblastoma (GBM) cells in which long-term exposure to morphine has inhibitory effects [35]. Furthermore, Friesen *et al.* demonstrated that D,L-methadone sensitized GBM cells to doxorubicin-induced cell death via activation of caspases which led to tumor growth reduction in rodents [36]. Prostate cancers cells also express MOR and modify their function after being exposed to opioids. An in vitro study by Kampa *et al.* showed that opioid agonists caused dose-dependent inhibition of cell growth but this effect was drug- and cell line specific. For instance, etorphine had stronger inhibitory effects than morphine in both PC3 and LNCaP cell lines (hormone sensitive) but not in DU145 cells (hormone insensitive) [37]. Interestingly, the antitumor properties of these opioid agonists were not always fully reversed by the use of opioid antagonists, thus indicating a potential MOR independent effect [37]. In gastric cancer cells, sufentanil has shown dose dependent anti-proliferative effects via induction of cell arrest in G2/M phase [38]. In line with this finding, down regulation of the MOR is associated with reduced tumor progression in a mouse model of liver cancer, despite

evidence from in vitro experiments indicating that morphine and endomorphines -1 and -2 does not affect cell proliferation in SK-HEP-1 cells [39, 40]. It is worth mentioning that exogenous opioids appear to have no effect on migration and chemotaxis of pancreatic cancer cells (PANC-1) [41].

In summary, most of the experimental studies that investigated the direct effect opioids on cancer cells (with exception of non-small cell lung cancer cells) have demonstrated predominant antitumor properties, however the different effects on cancer cell proliferation, migration and invasion appear to be not only cell type and opioid dependent but also dosage and experimental conditions (in vivo or in vitro and acute or chronic administration) dependent [42].

Effect of opioids in tumor microenvironment

Over the last years, it has become evident that cancer cells need the interactions and crosstalk of supporting cells from the tumor microenvironment in order to proliferate and invade [43]. Opioids have shown effects on at least 2 of the 3 components of the stromal cells tumors including angiogenic vascular cells (endothelial cells) and infiltrating immune cells (CD4 and 8 T-cells, natural killer [NK] cells and B cells) [44]. Therefore, some of the results observed in in vivo experimental conditions and in human studies can also be explained by the effect of opioids in the tumor microenvironment (Figure 1).

The effects of opioids in angiogenesis are complex. Short-term exposure of human umbilical vein cells to physiological concentrations of endomorphin-1 and -2 has shown to increase cell proliferation, migration and adhesion but has inhibitory effects at high concentrations [45]. The mechanism behind opioid-induced angiogenesis is still a matter of extensive investigations but it appears to involve Src-mediated VEGF receptor transactivation and activation of STAT3 [46-48]. In line with this evidence, subacute exposure of injured tissues to fentanyl is associated with increase angiogenesis and lymphangiogenesis via interaction with platelet-derived growth factor receptor (PDGFR-β) and modulation of nitric oxide [49]. On the contrary, long-term administration of morphine inhibits tumor cell–induced angiogenesis in mice. This phenomenon can be explained by a reduction in the recruitment of neutrophils that are able to not only produce angiogenesis factors and but also induce suppression in the release of endothelial progenitors [50, 51].

Immune infiltrating cells are important components of the tumor microenviroment. The impact of opioids on cells that participates in innate and adaptive immune responses against tumors remains unclear because the experimental settings in which opioids have been tested are different (in vitro versus in vivo, acute versus chronic exposure). For instance, while the short-term infusion of low doses of fentanyl in healthy subjects not having surgery has shown to increase the function of circulating NK cells, intermediate-to-large doses of this opioid in patients undergoing surgery and those in intensive care unit have demonstrated a suppressive effect on the function of those cells [52-54]. On the other hand, the chronic administration of opioids to patients did not cause detrimental effect in the function of circulating NK cells compared to opioid-naïve subjects [55]. There is no evidence suggesting that the intrathecal administration of opioids has protective effects on the immune system. In fact, it has been suggested that the opioid-induced immune suppression can result from a direct effect of opioids on lymphocytes or indirectly by activation of MOR located in central nervous system [56, 57].

Migration of NK cells into the tumor microenvironment is an essential step since these cells exert their anti-tumor effects mainly by direct cytotoxicity. Recent experimental data indicates the NK cells are present in larger number in tumors of MOR-/- mice in comparison to wild type animals; thus, suggesting a potential inhibitory effect of MOR activation in the migratory activity of NK cells [58]. Koodie *et al.* have investigated the effects of morphine in tumor-infiltrating leukocytes (TILs) and found that the long-term administration of this opioid diminished leukocyte migration in solid tumors [50]. In line with these findings, another group of investigators demonstrated that the density of CD-4 and CD-8 lymphocytes was significantly reduced in tumors developing in MOR-/- mice; thus, suggesting that TILs presence in the tumor microenvironment is regulated by MORs [58].

Regulatory T-cells (Tregs), myeloid-derived suppressor cells (MDSCs), and their derivatives suppress the proper immune reaction to tumor cells and promote their proliferation. Although, it remains unknown about the impact of opioids in those cells, recent evidence indicates that the frequencies of immunosuppressive $CD4^+CD25^{high}$ Tregs are increased within the $CD4^+$ T cell compartment of peripheral blood of chronic heroin users [59]. Similarly, the administration of the synthetic opioids (sufentanil and fentanyl) is associated with a significant increase in Tregs in women undergoing breast cancer surgery [60].

It is well documented that opioids have suppressive effects on macrophages exposed to inflammatory stimuli. For instance, morphine and other opioids reduce the phagocytic and antigen presenting activities of macrophages as well as their capability of producing interleukin (IL)-1, IL-23 and tumor necrosis factor alfa (TNF-α) when they are stimulated with lipopolysaccharide [61-63]. Unfortunately, there is not much evidence on the effect of opioids in tumor infiltrating macrophages; however, Khabbazi *et al.* have shown that when

macrophages are co-cultured with breast cancer cells, morphine reduces the presence of M2 polarization and tumor aggressiveness [13].

In summary, opioids appear to have predominantly pro-angiogenesis and immunosuppressive effects in the tumor microenvironment.

Human studies

Only few human studies have investigated either the impact of opioids per se or the relevance of expression of MORs in tumors on oncological outcomes (Table 1). In patients with NSCLC, 4 retrospective studies have indicated an association between the use of opioids and poor recurrence free- and/or overall survival [7, 64-66]. Three of these studies evaluated the use of opioid in the perioperative period and one was conducted in patients with advanced disease [7, 64-66]. Furthermore, recent evidence suggests that IL-6 gene polymorphism in patients with NSCLC can be linked to opioid consumption. Briefly, patients with IL-6 -174C/C polymorphism not only require the highest amount of opioids for analgesia but also had the shorter survival in comparison to those with IL-6 -174G/C and IL-6 -174G/G polymorphisms [67]. Contrary to these studies, Minami *et al.* found that the use of opioid was not a predictor of survival in palliative patients with lung cancer [68].

In patients who had radical prostatectomy, Scavonetto *et al.* found that a reduction in the use of perioperative fentanyl was not associated with longer recurrence free or cancer-specific free survival [69]. On the contrary, Forget *et al.* demonstrated that the use of sufentanil during surgery was associated with a 7-fold increase in the risk of cancer recurrence after radical prostatectomy [70]. In line with Forget's finding, Zylla *et al.* showed that the degree of MOR expression (low versus high) in prostate cancer specimens was a predictor of survival in patients with advanced disease. Moreover, those patients with greater opioid requirements showed shorter progression-free and overall survival [8].

Researchers have also investigated the impact of MOR expression and opioid use in other cancers. A recent study suggests that the expression of MOR is an independent risk factor for the presence of metastatic node disease in patients with esophageal cancer. Briefly, those patients with a higher cytoplasmatic expression of MOR had a higher incidence of N1 and N2 metastatic disease but not shorter survival than those with no or low expression of the receptor; although it is worth mentioning that the study include a small number of patients [71]. In line with these findings, Heirinch *et al.* found that despite a significant reduction in opioid consumption in patients who had epidural analgesia, their survival was similar to those who had a larger use of opioid and no regional analgesia [72].

In women with ovarian cancer, de Oliveira el al demonstrated that the use of intraoperative and postoperative neuraxial analgesia and anesthesia respectively, was associated with longer disease free survival in comparison to intravenous opioids and postoperative epidural treatment. In this study, the authors demonstrated that patients who had intraoperative and postoperative neural analgesia and anesthesia had the lowest consumption of opioids; however, opioid consumption was not included in the analysis to evaluate the impact on cancer recurrence as an independent variable [73].

Three different groups of investigators have studied the impact of opioids on breast cancer recurrence. On the one hand, Exadaktylos *et al.* reported that patients who had regional anesthesia/low consumption of opioids during breast cancer surgery showed a lower rate of cancer recurrence than those who had an opioid/sevoflurane analgesia/anesthesia technique [74]. On the other hand, a large cohort study did not support the association between the use of opioids and shorter survival [75]. Similar results were reported by Forget *et al.* who could not demonstrate an association between the use of sufentanil and cancer recurrence after mastectomy [76]. To complicate matters further, 2 studies have shown that female A118G allele carriers had either an increased or reduced breast cancer risk in comparison to both healthy female or the entire control group of patients [77, 78].

Lastly, our group found that the use of intraoperative opioids was an independent factor of disease progression in patients that undergo surgery for squamous cell carcinoma of the larynx [9].

Conclusions

MORs are expressed in a wide variety of cancer cells and in cells that are part of the tumor microenvironment. Although, the evidence still remains controversial, most experimental and clinical studies suggest that an increased expression of MOR in malignant NSCLC cells and the use of large doses of opioids during NSCLC surgery or in patients with advanced disease are independent risk factors for cancer recurrence or progression. However, it is worth mentioning that until a higher quality of scientific evidence from clinical studies is available, the use of opioids to provide analgesia perioperatively or in patients with advanced cancer disease should be part of routine clinical care.

Conflicting interests

The authors have declared that no competing interests exist.

Author contributions

JPC was involved in reviewing the literature; writing of the manuscript and final approval. DB, MM, MDG and MA were all in writing of the manuscript and final approval.

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