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The role of analgesics in cancer propagation

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The treatment of cancer pain is paramount to both medical practitioner and patient in order to maximize quality of life. Cancer pain results from direct tumor effects as well as from surgical and medical treatments. Despite therapeutic advancements, morbidity and mortality in cancer care remains high, often from local recurrence or metastasis. Increasing evidence suggests analgesics affect the cellular milieu of malignant and nonmalignant cells and may influence cancer outcomes by directly stimulating tumor growth and inhibiting immune surveillance. Opioids have been shown to cause immunosuppression and stimulate malignant cells in vitro, though adjunct analgesics may additionally promote tumor cell growth. These results have led many to hypothesize that regional analgesic techniques may offer survival advantages to systemic analgesics. Thus far, the data do not support specific analgesic recommendations for the cancer patient, though ongoing prospective, randomized clinical trials are under way to better characterize the safest analgesic regimens for cancer patients.

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Introduction

Cancer treatment and cancer pain management are major health burdens worldwide. In 2008, 13% of all deaths worldwide and 25% of deaths in the United States were attributable to cancer. In the same year, an estimated 12.7 million new cases of cancer were diagnosed and by 2030, this number is projected to grow to 22 million new cases annually [1]. Despite many advances in cancer treatment modalities including novel surgical techniques, chemotherapy, radiation, and immunotherapy, tumor recurrence and metastasis are common and mortality high. In an effort to improve these outcomes, researchers and investigators have begun to look at the effect of anesthetics and analgesics on cancer biology and cancer outcomes.

The anesthesiologist's role in cancer pain management has historically focused on the treatment of acute surgical pain at the time of resection and refractory chronic pain from disease burden and therapy. Though most cancer patients will interact with an anesthesiologist for only a short period of time during treatment, recent reviews suggest that perioperative techniques and analgesics may stimulate cancer cells and suppress host anticancer immunity [2–5]. As such, the safety of analgesics in these patients has come under increasing scrutiny.

Analgesic agents are a diverse group of medications with multiple effecter sites in the human body and, as such, several mechanisms by which analgesics may worsen cancer outcomes have been suggested [2–5]. Many analgesics cause immunosuppression of the innate and humoral defense systems, which the body relies upon for cancer regulation. Of particular interest has been the suppressive effects of many different analgesics on natural killer (NK) cell function, a subgroup of the innate immune system responsible for lysing metastatic cancer cells and the primary host defense against malignant spread [6]. Analgesics additionally exert negative effects on the endocrine system further diminishing host tumor response. Finally, there are growing data on the direct effects of analgesics on cancer cell function and propagation, leading some to question the safety of certain systemic analgesics in cancer patients.

These investigations have prompted research into the potential benefit of regional anesthesia in cancer patients to prevent metastasis and improve cancer outcomes by limiting systemic analgesic exposure. This research is complicated, however, by data which demonstrate that both surgery and inadequately treated pain cause immunosuppression and are suspected to influence metastasis and recurrence [7].

The following is an evidence-based review of the influence of analgesics and postoperative pain modalities on cancer cells and cell-mediated immunity with specific interest in human studies demonstrating cancer outcomes based on postoperative and cancer pain management.

A literature search of PubMed© until June 2013 of the terms "anesthesia and cancer recurrence," "anesthesia and tumor progression," "opioids and cancer progression," "cox inhibitors and cancer," "regional anesthesia and cancer outcomes," "alpha agonists and cancer," "pain and immunosuppression," "endocrine effects of opioids," and "nonsteroidal anti-inflammatory drugs (NSAIDs) and cancer" were used as the sources of information for this article. Pertinent references from the reviewed articles were additionally included.

Opioid analgesia

Overview

Opioid pharmacotherapy has served as a mainstay of the treatment of cancer and surgical pain since morphine was isolated by Serturner in 1803 [8]. Our knowledge of opioids has expanded to the refinement of natural (codeine and morphine), semisynthetic (oxycodone and hydrocodone), and fully synthetic (fentanyl, methadone, and tramadol) opioids. Four different opioid receptors (mu, delta, kappa, and nociceptin) are expressed in the body with endogenous and exogenous opioid binding in the central nervous system (CNS) modulating downstream effectors and the perception of pain [6]. In the past 15 years, there has been a flurry of studies investigating the effects of opioids on tumor cell growth via direct (receptor stimulation) and indirect (immunosuppression and endocrine modulation) pathways.

Effect of opioids on the immune and endocrine system

It has been demonstrated for some time that in addition to their analgesic effects, opioids decrease cellular immunity in both human and animal models [9]. Opioids have been shown to affect nearly all aspects of the immune system including macrophages, neutrophils, T cells, and NK cells [10,11]. Cellular immunity, the system primarily responsible for host antitumor defense, is suppressed with both acute and chronic opioid exposure [9]. Table 1 reviews animal and human study effects of opioids on the innate and adaptive immune system.

Opioid-related immunosuppression is likely not a class effect but agent specific and independent of the antinociceptive effect [9]. Morphine, codeine, and fentanyl have each been shown to suppress NK cell function [12]. Subsequent analysis of other opioids has revealed controversy with studies demonstrating unchanged, impaired, and even improved immunologic effects with methadone and buprenorphine. [11] Sacerdote et al. (1997) demonstrated that, unlike morphine and fentanyl, hydromorphone and oxycodone did not decrease NK cell activity in mice models despite being more potent analgesics. The authors hypothesize that this difference may be due to the variable carbon side chains of these semisynthetic opioids [9]. Using rat models, Francini et al. (2007) demonstrated that morphine and fentanyl not only suppress NK cell function but also increased pulmonary adenocarcinoma metastasis in mice undergoing surgery [13]. Buprenorphine conversely (a partial mu-opioid receptor (MOR) agonist) did not demonstrate any immunosuppressive effects on NK cell function and reduced the number of lung metastases in mice following surgery compared to controls in the morphine and fentanyl groups [13]. Despite much data on murine models, in vivo evidence is sparse as the majority of published human data focus on the perioperative period that is confounded by the immunosuppressive effects of surgery and pain itself. Convincingly, Brown et al. (2012) demonstrated the immunosuppressive effects of morphine in two different nonhuman primate lines with good interspecies reproducibility, possibly through decreased intracellular energy metabolism in T cells [11]. This work is promising to help clarify the significance of conflicting murine models. Thus, while the immunosuppressive effects of certain fentanyl, codeine, and morphine have been well documented, controversy exists as to the true immunomodulatory effects of others.

Opioids additionally exert complex effects on the endocrine system. Table 1 summarizes pertinent animal and human studies, though the effects are not uniform across species. Single-dose opioid exposure has been shown to suppress adrenocorticotropic hormone (ACTH) and cortisol levels at baseline and after corticotropin-releasing hormone (CRH) stimulation in humans [14]. Frank adrenal insufficiency after opioid exposure has been reported in several case reports after hydromorphone [15], fentanyl [16], and methadone [17]. This suppression is postulated to support tumor growth and potentiate malignant metastasis.

Direct effects of opioids on tumor progression

It is postulated that direct stimulation of the MOR by exogenous opioids affects tumor growth likely through upregulated angiogenesis [18,19]. Increasing cell culture and animal studies support the theory that opioids exert pro-angiogenic effects on tumor cells. Lennon et al. (2012) demonstrated that synthetic opioids stimulate endothelial cell migration and proliferation through vascular endothelial

Table 1
Immunomodulatory and neuroendocrine effects of opioids.

	Animal studies	Human studies
Innate immunity: [9,12,78,79]	•Decreased NK cell activity	•Decreased NK cell activity
Adaptive immunity: [80,81]	•Increased T cell apoptosis •Increased Thymic and splenic atrophy	
Neuroendocrine system: [82]	•Varying ACTH, CRH, and cortisol response to dose and duration of exposure •Increased GH and prolactin secretion •Decreased TSH secretion	•Decreased ACTH, CRH, and cortisol levels with possible adrenal suppression •Increased GH, prolactin, and TSH secretion •Hyperglycemia and impaired insulin secretion

NK cell = natural killer cell, GH = growth hormone, TSH = thyroid stimulating hormone, HPA = hypothalamic pituitary adrenal axis, ACTH = adrenocorticotropic hormone, CRH = corticotropin releasing hormone.

growth factor (VEGF) and angiogenic pathways [20]. Coadministration of methylnaltrexone (an opioid receptor antagonist) blocked this increased angiogenesis. Methylnaltrexone additionally exerted synergistic effects with bevacizumab, an anti-VEGF monoclonal antibody, on the inhibition of VEGF-induced angiogenesis in endothelial cells [21]. Gupta et al. (2002) demonstrated breast cancer cells transplanted into mouse models grow significantly larger and exhibit increased neovascularization when exposed to clinical doses of morphine. [22] This effect is even more pertinent as molecular and modern imaging techniques have demonstrated increased expression of opioid receptors in human cancer cells compared to normal tissue [23,24].

Opioids may directly inhibit tumor cells as well. Morphine has been shown to stimulate apoptosis in human cancer cell lines at both therapeutic and supratherapeutic doses [25,26]. Chronic morphine exposure in human breast cancer cells attenuates cell growth and increases tumor apoptosis [27]. Morphine has additionally been shown to inhibit adenocarcinoma cell progression and even promote cell death at high concentrations perhaps through a p53-mediated pathway [28]. This effect is not uniform, however, as Lin et al. (2007) demonstrated that morphine antagonizes the pro-apoptotic activity of doxorubicin (a chemotherapeutic anthracycline antibiotic), in neuroblastoma cell lines by inhibiting formation of reactive oxygen species (ROS) that initiate apoptosis [29]. In animals, Yeager and Colacchio (1991) demonstrated that intermittent morphine injections decreased tumor growth in a rat model of metastasizing colon cancer [30]. Thus, the direct effects of opioids on tumor cell apoptosis remain contradictory and controversial.

Most convincingly, the opioid receptor itself appears to regulate tumor growth in animal models. Overexpression of the MOR in human non-small cell lung cancer (NSCLC) more than doubled primary tumor growth rates in mice and increased lung metastasis by approximately 20-fold compared with controls [20]. Most strikingly, Mathew et al. (2011) demonstrated that mice with knockout MORs did not develop significant tumors when injected with human lung cancer cells as compared to controls. Subsequent silencing of the MOR in the control groups decreases metastasis by >70% [31]. These effects occurred in the absence of exogenous opioids suggesting that the MOR itself regulates tumor growth and metastasis with only endogenous opioid stimulation.

Human studies

Despite the numerous studies demonstrating the molecular effects of opioids on cancer cells and the immune system, there is no definitive evidence that opioids worsen outcomes in cancer patients. A study looking at the efficacy of implantable intrathecal pumps in terminally ill cancer patients demonstrated a trend towards improved outcomes in the intrathecal vs. systemic opioid group. Patients receiving intrathecal opioids had a survival rate of 54% compared to 37% in those receiving systemic opioid analgesia though not significant ($p = 0.06$) [32,33]. There are many explanations for this trend towards improved survival, including higher quality of life and the benefit of improved pain control with the intrathecal pumps. Recently, different opioid receptor polymorphisms themselves have been associated with differing cancer outcomes suggesting again a direct effect of the receptor in cancer regulation. A polymorphism of the MOR at A118G is associated with decreased opioid binding and reduced analgesic response to opioids [34]. Bortsove et al. (2012) demonstrated in a retrospective study that patients who express the G allele (AG or GG: 5% of African American and 24% European American Women) demonstrated decreased breast cancer-specific mortality ($p = 0.001$), though this benefit was limited to cases of invasive disease. The A/A genotype was associated with a 17% mortality compared to 8% of women with the G allele (AG or GG) ($p < 0.001$) [35]. Thus, while there is retrospective evidence in humans for the influence of the MOR in cancer outcomes, the effects of opioids themselves have not been shown to be detrimental beyond their known side effect profile.

Adjunct analgesics

Ketamine

The analgesic and dissociative effects of the NMDA receptor antagonist ketamine have been used as an adjunct in the treatment of cancer pain for decades. Recently, the use of ketamine in cancer patients

has come under scrutiny, as Hardy et al. (2012) demonstrated in a randomized double-blinded trial that adjunct ketamine for refractory cancer pain provides minimal additional analgesia (number needed to treat 25) but was associated with increased occurrences of adverse events such as nausea, vomiting, and confusion (number needed to harm six) [24]. A subsequent Cochrane review (2012) concluded that current evidence is insufficient to assess the benefit or harm of ketamine as an adjunct to opioids in oncologic pain [36]. Despite this controversy, ketamine remains a potent analgesic and has found routine use in refractory pain and unique clinical scenarios. Research on the effects of ketamine on cancer pathogenesis has been limited. Animal studies by Malamed et al. (2003) demonstrated immunosuppressive effects of ketamine decreasing both number and efficacy of NK cells. Rats injected with human cancer cells while exposed to ketamine had 5.5 times the number of tumor cells compared to controls [37]. No human to date has addressed the risk of recurrence or metastasis with patients receiving ketamine for cancer pain.

Alpha-2 agonists

Though initially described as an antihypertensive, the alpha-2 agonist clonidine has been used for decades as an adjunct in peripheral and neuraxial anesthesia to prolong surgical and chronic pain relief. The newer selective alpha-2 agonist, dexmedetomidine, has been approved for use in the ICU and operating room as a sedative, but is known to exert analgesic effects similar to clonidine and its intrathecal efficacy has been recently described [38]. Intravenous (IV) dexmedetomidine has additionally been described as an adjuvant analgesic for refractory cancer pain [39]. As patents on dexmedetomidine expire, its off-label use for pain will likely only increase. NK cells have been shown to express alpha-receptors and in vitro exposure to clonidine modulates NK cell function, increasing their cytotoxicity [40]. Conversely in mice, subhypnotic doses of dexmedetomidine downregulates antitumor host immunity via a decrease in theTH-1/TH-2 ratio and decreased IL-12 production and cytotoxic T-cell lymphocyte activity [41]. Breast cancer cells have additionally been shown to express alpha-receptors [42]. Incubation of these breast cancer cells with clonidine and dexmedetomidine demonstrated significant tumor growth compared to controls, and interestingly, treatment with yohimbine and rauwolscine (alpha receptor antagonists) completely reversed the effects of clonidine. [43] No human studies have yet been published on the effects of alpha-agonists on cancer outcomes or tumor growth. As such, it remains too early to make recommendations for their use in cancer patients, but caution should be employed as their use increases for their analgesic properties.

Nonsteroidal anti-inflammatory drugs

NSAIDs are effective analgesics for the treatment of mild to moderate pain. When used in conjunction with opioids, NSAIDs reduce opioid requirements and alleviate opioid side effects [44]. Tumor cells are postulated to evade host antitumor immune systems by prostaglandin-mediated immunosuppression and IL-12 downregulation [45]. Attenuating prostaglandin synthesis via inhibition of cyclooxygenase enzymes, NSAIDs are thought to be ideal agents to suppress this immune evasion by tumor cells [6,46]. Likewise, the immunosuppressive effects of surgery that cancer patients experience following tumor resection is additionally thought to be mediated by prostaglandins and catecholamine release [47].

Animal studies have demonstrated attenuation of the immunosuppressive effects of opioids when used in conjunction with NSAIDs. Using a rat model, Farooqui et al. (2007) demonstrated that celecoxib (a selective COX-2 inhibitor) reversed morphine-induced stimulation of COX-2, PGE-2, and angiogenesis [48]. Inhibition of COX-2 additionally reversed the morphine-induced growth and metastasis improved mortality [48]. These data have led some practitioners to recommend the use of COX-2 inhibitors when utilizing opioids for cancer pain relief to vitiate hypothesized negative opioid effects [2].

COX-2 receptors are overexpressed in several different tumor types including breast, lung, and colon cancer cells [49]. Greater than 80% of human colorectal cancers overexpress COX-2 receptors and its expression may be associated with inferior survival [50]. A recent meta-analysis by Kunzmann et al. (2013) demonstrated that COX-2 receptor expression in colorectal cancer is associated with an increased risk of recurrence and poorer colorectal cancer-specific survival [51]. Randomized trials of

selective COX-2 inhibitors celecoxib and rofecoxib reduced the risk of developing colorectal adenoma risk by as much as 45%, but cardiac toxicity and increased thrombotic events have limited its use as a chemopreventive agent [52–54]. A meta-analysis by Rothwell et al. (2010) additionally demonstrated a reduction in colon cancer risk and mortality (24% and 35%, respectively), in patients taking a daily aspirin (a nonselective COX-1 and COX-2 inhibitor) dose of at least 75 mg, further supporting the prostaglandin-mediated tumorigenesis and immune evasion hypothesis [55]. At this time, the use of NSAIDs is limited due to the increased bleeding risk and gastritis associated with nonselective inhibitors and the increased cardiovascular risks associated with selective COX-2 inhibitors. Despite these risks, NSAIDs are unique among the analgesics with clear human evidence for cancer preventive effects and possible antitumor effects.

Regional analgesia

Local anesthetics

Since Koller performed the first operation under local anesthesia using cocaine, local anesthetics have remained a mainstay in the treatment of surgical, local, and chronic pain [56]. In addition to their antinociceptive properties, local anesthetics provide direct inhibition of cancer cell proliferation [57,58]. Lidocaine, bupivacaine, and ropivacaine (amide local anesthetics) inhibit mesenchymal stem cell proliferation, which are used as a model for tumor spread and may play an active role in both tumor growth and metastasis formation [59]. Lidocaine has additionally been shown to inhibit in vitro cell migration of lung adenocarcinoma cells [60]. Ropivacaine also inhibits migration of in vitro lung adenocarcinoma cells and has additionally been shown to inhibit human colon adenocarcinoma cells in a dose-dependent manner [52–54]. While research remains limited, the effect of local anesthetics on tumor cells appears to be agent specific with 2-chloroprocaine (an ester local anesthetic) having no effect on in vitro lung adenocarcinoma cell migration [60]. To date, human studies looking at the safety and potential benefit of local anesthetics have explored the benefit of regional anesthesia using local anesthetics to systemic opioids.

Regional anesthesia

The immunosuppressive affects of opioids and antitumor effects of local anesthetics have led some to postulate that the treatment of surgical and cancer pain by regional anesthesia methods may improve cancer outcomes [61]. The proposed mechanism for this benefit is twofold. By limiting potential exposure to systemic analgesics, regional anesthesia may avoid the immunosuppressive and proposed direct cancer-stimulating effects of these systemic medications. Additionally, regional anesthesia may reduce the immunosuppressive effects of surgery itself. Synder and Greenberg (2010) [6] nicely review the immunosuppressive effects of surgery in their paper, highlighting the inhibition of NK cell function [62] and the upregulated neuroendocrine and sympathetic responses which, in turn, downregulates cellular immunity [63]. Neuraxial anesthesia (spinal or epidural regional anesthesia) blunts the sympathetic response to surgery by preganglionic sympathetic denervation, thus minimizing the surgical "stress response" and potentially its adverse effects on the immune system [6,64]. O′ Riain et al. (2005) demonstrated that like neuraxial anesthesia, paravertebral regional anesthesia (PVAA) additionally dampen surgical stress response in breast cancer patients, but interestingly did not alter expression of pro-tumor growth factors such as VEGF and PGE-2 [65]. As such, the benefit of regional anesthesia has garnered significant interest by research clinicians.

Greater than a dozen studies have been published on the effects of regional anesthesia vs. general anesthesia and postoperative opioid analgesics on cancer recurrence and metastasis. Most studies have focused on the perioperative period during tumor resection to evaluate the benefit of regional anesthesia in cancer outcomes. Confounding these study designs, most investigations include patients undergoing surgical resection under general anesthesia, which is associated with immunosuppression and the potential for increased tumor metastasis [2–5]. Furthermore, the majority of these studies are retrospective with conflicting benefits of regional anesthesia on different cancer types. These results are summarized in Table 2. Given the retrospective nature of these studies, there is the inherent risk of selection and information bias confounding results.

Table 2
Recent retrospective studies on the effects of regional anesthesia and cancer recurrence.

Author	Year	Cancer type	Number of patients	Outcome
Day et al. [83]	2012	Colorectal (Laparoscopic resection)	424	No significant difference in OS ($P = 0.622$) or DFS ($P = 0.490$) at 5 yr
Gottschalk et al. [84]	2012	Malignant melanoma lymph node dissection	275	Non-significant trend ($p = 0.087$) in survival in spinal anesthetic group
Lai et al. [85]	2012	Hepatocellular carcinoma	179	GA was associated with reduced risk of cancer recurrence HR: 3.66 (95% confidence interval [CI], 2.59–5.15; $P < 0.001$)
Cummings et al. [66]	2012	Non-metastatic colorectal cancer	42,151	Improved 5-yr survival (61% vs. 55% $p = 0.001$) with EA but no difference in cancer recurrence rates
De Oliveira et al. [86]	2011	Ovarian cancer debulking	182	Delay to time of recurrence with intraoperative EA (73 vs 38 mo. $P = 0.002$) but not with exclusive post-operative EA groups (33 vs. 38 mo. $P = 0.92$)
Lin et al. [87]	2011	Ovarian carcinoma	143	Improved survival with EA vs. GA at 3 and 5 years ($P = 0.043$)
Gupta et al. [88]	2011	Colon/rectal cancer	655	No difference in mortality between EA and PCA in colon cancer. Reduced rectal cancer mortality with EA vs PCA ($P = 0.049$)
Ismail et al. [89]	2011	Cervical Cancer	132	No benefit to neuraxial analgesia in mortality or recurrence in patients having brachytherapy for cervical cancer.

EA = epidural anesthesia, PVAA = paravertebral anesthesia, PCA = patient controlled analgesia, OS = overall survival, DFS = disease free survival, HR = hazard ratio.

Mao et al. (2013) recently published a meta-analysis of available studies comparing adjunct regional anesthesia in cancer surgery to standard postoperative opioids [4]. Fourteen studies were identified that compared the effect of epidural anesthesia (EA) (with or without general anesthesia) to general anesthesia (GA) alone, with 12,000 cases in the epidural group and 35,000 cases in the general anesthesia group. The study end points were overall survival (OS) and recurrence-free survival (RFS) analyzed using a random-effects model. An OS benefit to EA was demonstrated with a hazard ratio of 0.84 (95% CI 0.74–0.97, $P = 0.013$). These results remained significant when the largest retrospective study (Cummings et al. (2012)[66]) was excluded for concern that the large sample size would dominate other study outcomes. RFS was not demonstrated, however, with a hazard ratio of 0.88 (95% CI 0.64–1.22, $P = 0.457$). A subgroup analysis of colon and rectal cancer studies (the most commonly studied cancer type) again showed an OS benefit to EA over GA (HR = 0.65, 95% CI 0.43–0.99, $P = 0.045$). RFS was again not demonstrated in those patients receiving EA in either the colon and rectal cancer subgroups or prostate cancer subgroup. It is surprising that an OS benefit was demonstrated by this study but that RFS was not associated with EA. The authors comment that the benefit of neuraxial anesthesia on OS has been demonstrated in randomized control trials (RCTs) and cohort studies of patients without malignancy as well, thus suggesting the survival benefit was not due to cancer effects of the anesthetic technique but other inherent effects of regional anesthesia [67]. As such, this conflicting conclusion further illustrates the need for additional prospective studies to better characterize the benefit of regional anesthesia in cancer outcomes.

To date, three prospective studies have investigated the benefit of regional anesthesia in patients undergoing surgical cancer resection. Myles et al. (2011) conducted the largest published prospective RCT (MASTER trial) evaluating the survival benefit of regional anesthesia for pain control in patients undergoing abdominal surgery for resection of malignancy [68]. This multicenter study expanded on the data collected in the original MASTER trial (2002) [69] which randomized patients to either general anesthesia with adjunct EA or general anesthesia with traditional opioid patient-controlled analgesia (PCA) pain control. The original trial compared post-oncologic surgical morbidity and mortality in EA

Table 3
Prospective studies on the effects of regional anesthesia and cancer recurrence.

Author	Year	Cancer type	Number of patients	Outcome
Myles et al. [68]	2011	Abdominal malignancies	506	No difference in OS or time to recurrence between EA and controls.
Tsui et al. [90]	2010	Prostate cancer	99	No benefit to EA in DFS at 4.5 years.
Christopherson et al. [70]	2008	Colon cancer	177	Improved survival with EA before 1.46 years in patients without metastasis ($p = 0.012$) No benefit after 1.46 years or if metastasis

EA = epidural anesthesia, OS = overall survival, DFS = disease free survival.

and PCA groups, showing no difference between the groups though it did demonstrate improved pain scores and a lower incidence of respiratory failure in the EA group. Myles et al. compared cancer survival rates in these two groups 15 years after the original trial. Long-term follow-up failed to demonstrate a difference in cancer-free survival between the groups. RFS was additionally similar in both the EA and control groups, though it should be noted that the intention of the original MASTER trial was not to evaluate cancer survival outcomes. Supporting evidence for the benefit of regional anesthesia came from Christopherson et al. (2008) [70] who demonstrated an improved survival benefit to EA while undergoing surgical resection of colon cancer. This benefit extended only to 1.46 years and was demonstrated only in patients without metastasis ($p = 0.012$). After 1.46 years, or if metastasis were present, no benefit to EA was seen. The overall prospective data to date are listed in Table 3. Given the discrepancy between both retrospective and prospective studies, further studies are needed to determine and evaluate the effect of regional anesthesia on cancer outcomes. Table 4 lists prospective, randomized trials under way.

Effect of pain

The World Health Organization (WHO) currently estimates that 5.5 million people worldwide receive minimal or no analgesia for their cancer pain, though these data are limited by a lack of global

Table 4
Ongoing prospective, randomized clinical trials evaluating the benefit of regional anesthesia for cancer pain as listed at clinicaltrials.gov search terms: regional + anesthesia + cancer + recurrence.

Title	Cancer type	Study design number enrolled	Primary outcome	Estimated completion
Regional anesthesia and breast cancer recurrence NCT00418457	Primary localized breast cancer	Prospective RCT $N = 1100$	CR	March 2015
The effect of adding intraoperative regional anesthesia on cancer recurrence in patients undergoing lung cancer resection NCT011799308	Primary non-small cell lung cancer	Prospective, double blinded, RCT $N = 1532$	DFS	August 2018
Epidural or patient-controlled analgesia for colorectal cancer surgery. long-term outcomes. NCT01318161	Colorectal cancer	Prospective RCT $N = 300$	All cause mortality	December 2018
Anesthesia and cancer recurrence in malignant melanoma NCT01588847	Lower limb malignant melanoma	Prospective Single blind RCT $N = 230$	OS	March 2019
Regional anesthesia in colon rectal surgery NCT00684229	Primary colon cancer without known extension beyond colon	Prospective, double blinded RCT $N = 2500$	CR	December 2022

RCT = randomized control trial, OS = overall survival, DFS = disease free survival, CR = cancer recurrence.

cancer registries and instead relies on epidemiologic estimates [71]. In response to this pain epidemic, the WHO published cancer analgesia guidelines utilizing a "Three-Step Analgesic Ladder" algorithm [72]. Per this recommendation, initial management should utilize non-opioid analgesics, followed by opioids, then adjunct analgesics [72]. Should definitive evidence emerge for the harmful effects of opioids in cancer patients, modification of these recommendations will put people worldwide at further risk of substandard pain control. The adverse effect of inadequately controlled pain on cancer progression must be considered if future practice guidelines endorse one analgesic method over another in cancer patients.

In addition to the psychological and social harm of inadequately treated pain, the physiologic effects are thought to be deleterious. Inadequately treated pain alters the hypothalamic–pituitary Axis (HPA) causing sympathetic stimulation and immunosuppression. Stress additionally appears to negatively affect cellular immunity and NK cell function. Anderson et al. (1998) demonstrated that stress in women with breast cancer reduced NK cell lytic capabilities [73]. Uncontrolled pain additionally leads to the production of endogenous opioid including endorphins and endomorphines. Inflammation at sites of pain recruits opioid-containing leukocytes that release endogenous opioids [74]. The potential pro-malignant effects of exogenous opioids discussed above are additionally shared by endogenous opioids [18]; thus, uncontrolled pain itself may contribute to tumor growth and risk of recurrence.

Live animal models of breast cancer have shown that adequate analgesia (intrathecal or systemic opioid) increased length to recurrence of disease suggesting an effect of pain on metastatic spread [7]. In humans, a prospective analysis of patients with widespread or regional pain over an 8-year period demonstrated increased cancer-related deaths in both the intermediate and long term [75]. Prospective trials are limited for the obvious moral implications of undertreating pain. Indirectly, Lillemore et al. (1993) performed a prospective RCT in patients with terminal pancreatic cancer, randomized to splanchnicectomy with alcohol vs. placebo saline. The group demonstrated not only improved pain control but also improved survival ($p < 0.0001$) after undergoing splanchnicectomy with alcohol compared to controls receiving saline. [76] Convincingly, implicating the effect of pain, patients who underwent the splanchnicectomy but had no pain from their disease prior to the procedure had no change in OS compared to control groups. It should be noted that the use of opioids in the control and treatment groups were not reported. A follow-up study by Wong et al. (2004) subsequently failed to demonstrate the same survival benefit in pancreatic cancer patients receiving neurolytic celiac plexus block (NCPB) compared to systemic opioids, though it was associated with improved analgesia [77]. Despite the improved pain control, there was no difference in opioid usage between the two groups. Thus, definitive prospective evidence for the OS benefit of improved pain control in humans is inconclusive. While human studies are difficult to conduct in this area due to the moral implications of undertreating pain, these animal and human studies sufficiently highlight the need for appropriate analgesia should future studies recommend one form of analgesia over another.

Summary

Analgesia in cancer care is a top priority amongst providers and patients second only to possible cure. Animal and in vitro studies have outlined pathways by which analgesics may expedite cancer recurrence and tumor invasion, though human studies are conflicting. Opioid analgesia has been shown to negatively influence both cell- and humoral-mediated immunity and the neuroendocrine system. In animal studies, opioids influence angiogenesis and may directly contribute to tumor invasion. Despite this evidence, clinical studies have not convincingly demonstrated adverse outcomes in patients receiving opioids for cancer pain. There are limited data evaluating adjunct analgesics such as ketamine and alpha-adrenergic agonists in cancer pain treatment, though again in vitro and animal studies suggest tumor-stimulating behaviors. COX-2 inhibitors and select local anesthetics appear to have antitumor effects. Regional anesthesia promises to limit systemic analgesic exposure but, thus far, prospective data have failed to demonstrate a convincing benefit. Retrospective data have demonstrated a modest survival benefit, but no reduction in metastasis or cancer recurrence.

It remains too early to make recommendations regarding the analgesic technique in the cancer patient, though prospective RCTs are ongoing. Paramount to any practitioner caring for cancer patients

is the adequate treatment of pain to maximize quality of life and minimize adverse effects of poorly controlled pain. While studies suggest the possible benefit of regional anesthesia and COX-2 agents, the uniform use of these techniques is not yet recommended. Perhaps with future prospective clinical trials and ongoing animal and in vitro studies, optimal analgesic regiments will be elucidated.

Practice points

- Opioids decrease cellular and humoral immunity, and negatively influence the neuroendocrine system.
- Opioids increase tumor angiogenesis and decreased apoptosis in in vitro and animal studies.
- Buprenorphine, hydromorphone, and oxycodone do not appear to modulate immune function.
- The adjunct analgesics ketamine, clonidine, and dexmedetomidine may directly stimulate cancer cells and be associated with increased metastases in animal models.
- Local anesthetics may directly inhibit tumor growth, though the effect is likely agent specific.
- Meta-analysis of retrospective data suggests an overall survival benefit to regional anesthesia, though there is no difference in cancer recurrence or metastasis.
- The most complete randomized prospective trial to date (MASTER trial) failed to demonstrate a benefit to regional anesthesia compared to systemic opioid therapy in colorectal cancer.
- Untreated cancer pain results in decreased cellular and humoral immunity and cancer progression in animal studies.

Research agenda

- The effect of adjunct analgesics such as ketamine, alpha-adrenergic agonists (clonidine and dexmedetomidine), and acetaminophen on cancer cells needs further study.
- The effect of neuropathic pain agents (e.g., gabapentin and amitriptyline) on cancer cells and the immune system warrants investigation.
- Prospective trials on the effect of opioids and cancer outcomes are warranted though feasibly difficult.
- The clinical benefit to concurrent prostaglandin-blocking NSAIDs with opioid analgesics needs further study.
- Further prospective RCTs are needed to determine the effect of regional anesthesia on cancer recurrence and possible survival benefit.

Conflict of interest statement

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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