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Morphine use in cancer surgery

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Morphine is the core of perioperative pain management. However, when it comes to cancer surgery the possibility that this drug might affect tumor recurrence and metastasis has raised concerns. The results of two recent retrospective clinical trials indicated that regional anesthesia/analgesia might be beneficial in prostate and breast cancer surgery. It was proposed that morphine could be responsible for the higher recurrence and mortality rate observed in the general anesthesia/opioid analgesia groups. Nevertheless, the results of several other retrospective studies and one randomized prospective trial failed to confirm any advantage for regional anesthesia/analgesia over general anesthesia and opioid analgesia. Moreover laboratory data on the effect of morphine on cancer are contradictory, ranging from tumor-promoting to anti-tumor effects. Considering that surgical stress and pain promote the recurrence and spread of cancer, choosing a proper analgesic strategy is of high significance. Although the question of whether morphine causes any harm to cancer patients remains unanswered, alternative analgesic regimens could be used concomitant to or instead of morphine to limit its potential adverse effects.

Keywords: morphine, regional, anesthesia, analgesia, cancer, surgery

PERIOPERATIVE MORPHINE AND CANCER

There has been increased interest surrounding the possibility that morphine should not be given perioperatively to cancer surgery patients. This followed two retrospective clinical studies showing that when regional (i.e., paravertebral or epidural) anesthesia/analgesia was used in patients undergoing surgery for either breast or prostate cancer, the rate of cancer recurrence, and/or metastasis was significantly lower than in patients undergoing general anesthesia with opioid analgesia. The follow-up period was 2.5–4 years for the breast cancer and 2.8–12.8 years for the prostate cancer study (Exadaktylos et al., 2006; Biki et al., 2008). One of the hypotheses proposed to explain these results has involved the opioid-sparing effect of regional anesthesia/analgesia, and the assumption that morphine could be at least in part responsible for the higher recurrence and mortality rate in the general anesthesia groups, which received opioid analgesia.

Opioids are a major class of drugs in pain management and morphine, as a potent agonist of the mu opioid receptor, is still the drug of choice from this family (Paice, 2003). The concerns regarding possible promoting effects of morphine on tumor growth and metastasis mostly originated from the fact that opioids, including morphine, have well-established immunosuppressive effects, compromising cellular and humoral immune function and thus host defense against malignancies (Ishikawa et al., 1993; Sacerdote et al., 2000; Franchi et al., 2007). In addition, morphine has recently been reported to increase angiogenesis, thereby supporting tumor growth in a breast cancer xenograft model in mice (Gupta et al., 2002). Further fueling the debate, opioids were shown to transactivate VEGF receptors, induce angiogenesis and promote vascular permeability (Singleton et al., 2006, 2007), and activation of opioid receptors was documented to enhance the proliferation and invasion of lung cancer cells (Mathew et al., 2011).

Whilst these reports are convincing and the question of whether morphine should be avoided in cancer surgery patients legitimate, it must be kept in mind that the reported tumor-promoting effect of opioids is balanced by their anti-tumor potential, documented at various levels (**Table 1**). Morphine has also been shown to have direct anti-proliferative and pro-apoptotic effects on different cancer cells (Maneckjee et al., 1990; Maneckjee and Minna, 1994; Hatzoglou et al., 1996; Sueoka et al., 1998; Tegeder et al., 2003; Zagon and Mclaughlin, 2003). Furthermore, several studies using endothelial cells (Balasubramanian et al., 2001; Lam et al., 2008; Hsiao et al., 2009), chorioallantoic membranes (Pasi et al., 1991; Blebea et al., 2000), *in vitro* capillary tube formation assay or implanted matrigel plugs (Lam et al., 2008; Martin et al., 2010a,b), and *in vivo* tumor assays (Koodie et al., 2010; Ustun et al., 2010), have demonstrated angiostatic effects for morphine. However there is no clinical study demonstrating the effect of morphine *per se* on tumor growth, recurrence or metastasis. Postoperative pain management is of high significance especially in cancer patients. Failure to properly control postoperative pain, results in an exacerbated, and prolonged stress response, which increases the risk of tumor spread in the postoperative period (Page et al., 2001). The highly effective analgesic effect of opioids is suggested to be beneficial in reducing the surgical stress (Yeager and Colacchio, 1991; Page et al., 1993, 1998; Sasamura et al., 2002). Therefore, if morphine analgesia is to be avoided in the perioperative period in cancer surgery patients, effective alternative strategies should imperatively be adopted to effectively control postoperative pain. These include (i) the use of regional anesthesia/analgesia, (ii) the co-administration with morphine of a peripheral opioid antagonist, or (iii) alternate analgesic interventions.

Table 1 | The effect of morphine administration on tumor progression in animal models.

Animal model	Type of cells	Impact of morphine administration on Tumor progression	Reference
I.V. injection of tumor cells to rats	MADB106 lung tumor cells	Increase of lung diffusion of tumor cells in the presence of surgical stress	Franchi et al. (2007)
S.C./I.P. injection of tumor cells to mice	EL-4 leukemia Sarcoma 180 carcinoma P388 leukemia Meth-A sarcoma	Increase in the weight of solid tumors and increased mortality caused by ascite-type tumors	Ishikawa et al. (1993)
Matrigel plugs and breast xenografts in mice	MCF-7 breast cancer cell	Increase in tumor size and angiogenesis	Gupta et al. (2002)
I.V. injection of tumor cells to mice	26-L5 colon carcinoma cells	Decrease in the number of metastatic colonies in lungs	Harimaya et al. (2002)
Tumor cell-containing matrigel plugs in mice	Mouse Lewis lung carcinoma cells	Reduction in tumor cell-induced angiogenesis	Koodie et al. (2010)
S.C. tumor xenografts in mice	Ehrlich ascites	Inhibition of tumor growth via suppression of tumor angiogenesis and increased tumor cell apoptosis	Ustun et al. (2010)
I.V. inoculation of tumor cells to rats	MADB106 breast cancer cells	Inhibition of surgery-induced increase in metastatic localization of tumor cells in lungs	Page et al. (1993, 1994, 1998)
I.V. injection of tumor cells to rats by laparotomy	Colon adenocarcinoma cells	Decrease in the incidence and burden of metastatic tumors in the liver	Yeager and Colacchio (1991)
I.V. injection of tumor cells to rats with laparotomy	Colon adenocarcinoma cells	Increase in the incidence and burden of metastatic tumors in the liver	Colacchio et al. (1994)
Tumor cell inoculation into hind paw of mice	B16–BL6 melanoma cells	Decrease in tumor growth and the number of metastatic nodules in the lungs 2 weeks after tumor excision	Sasamura et al. (2002)
S.C. injection of tumor cells in the right hind thigh	SCK mammary carcinoma cells	Increase in tumor angiogenesis Increase in tumor weight as well as incidence and burden of lung metastases	Farooqui et al. (2007)
I.V. injection of tumor cells to rats 4–5 h after induction of anesthesia (morphine administration) for laparotomy	MADB106 mammary adenocarcinoma cells	Attenuation of surgery-induced surge in lung retention of tumor cells 24 h after tumor cell injection No significant effect on the number of metastatic colonies in lungs after 3 weeks	Bar-Yosef et al. (2001)
S.C. injection of tumor cells to mice	MCF-7 and MDA-MB231 breast cancer cells HT-29 colon cancer cells	Smaller volume of MCF-7 and MDA-MB231 tumors compared to control groups No effect on the size of HT-29 tumors	Tegeder et al. (2003)

REGIONAL ANESTHESIA AND ANALGESIA

In animal models it has been demonstrated that epidural or spinal blockade results in a reduction of the immune suppression after surgery and protection against postoperative metastasis (Bar-Yosef et al., 2001; Wada et al., 2007). Recent retrospective studies have been conducted to unveil potential significant differences in cancer recurrence and or metastasis after surgery with regional or general anesthesia. Two retrospective studies on breast and prostate cancer showed that cancer recurrence rate was lower when general anesthesia was supplemented with regional (i.e., epidural or paravertebral) anesthesia. Exadaktylos et al. (2006) studied the medical history of 129 patients that had undergone mastectomy for primary breast cancer and found lower cancer recurrence and metastasis ∼2.5 years after surgery in patients that received paravertebral anesthesia with general anesthesia compared to those that had received general anesthesia alone (Exadaktylos et al., 2006). Similarly Biki et al. (2008) showed that in radical prostatectomy, using epidural anesthesia and analgesia was associated with a lower risk of biochemical cancer recurrence, identified as a postoperative increase in prostate-specific antigen (PSA), in a follow-up period of 2.8–12.8 years (Biki et al., 2008). In a partly supporting study, epidural anesthesia/analgesia complementary to general anesthesia was found to be associated with a longer survival rate in patients with non-metastatic (but not metastatic) colon cancer (Christopherson et al., 2008). However, other retrospective studies failed to show any benefits for regional anesthesia/analgesia regarding recurrence and mortality rate after surgery for prostate, colorectal, and cervical cancers even though it reduced the need for postoperative systemic opioid administration (Gottschalk et al., 2010a; Ismail et al., 2010; Tsui et al., 2010).

Clearly, and as acknowledged by the authors, retrospective studies suffer from a high rate of selection and confounding biases. Furthermore, these studies were designed to test different anesthesia and analgesia regimens rather than the effect of morphine, and the existence of multiple uncontrolled variables in the two groups made it difficult to attribute the observed results to morphine administration as an independent factor.

Samples from patients given general anesthesia with regional anesthesia/analgesia or opioid analgesia for cancer surgery have also been investigated for pro- or anti-tumor effects *in vitro*. Serum from patients of a prospective study, treated with a combination of general anesthesia with paravertebral anesthesia/analgesia, increased the proliferation but not the migration of cultured MCF-7 breast cancer cells when compared to general anesthesia and opioid analgesia group (Deegan et al., 2009). Furthermore, the postoperative serum concentration of pro-tumor cytokines, IL-1β and IL-8, and of the pro-angiogenic factor VEGF-C were considerably lower while anti-tumor cytokine, IL-8 was higher in breast cancer surgery patients treated with paravertebral anesthesia and analgesia rather than general anesthesia and opioid analgesia (Deegan et al., 2010; Looney et al., 2010).

The only prospective study with finalized and published results testing the effect of anesthesia and pain management on cancer recurrence and mortality is a multicenter randomized, controlled clinical trial performed in Australia, New Zealand, and Asia. In this study 503 patients undergoing major abdominal surgery for cancer, mostly colon cancer, were randomly assigned to receive general anesthesia with either epidural anesthesia and analgesia, or postoperative intravenous opioid analgesia. The results showed no significant difference in cancer recurrence and mortality at 2–3 years between the two groups (Myles et al., 2011), confirming the relative lack of effect seen with colon cancer in retrospective studies (Christopherson et al., 2008). The results of these clinical studies are summarized in **Table 2**. Several randomized controlled clinical trials are still in progress to assess the possible effect of anesthetic technique on the course of cancer, which might be tumor site-specific. These studies are following up the recurrence, metastasis, and mortality rates in patients randomized to receive either general or regional anesthesia/analgesia for surgical removal of different types of cancer in multiple clinical centers (Gottschalk et al., 2010b; Afsharimani et al., 2011). Whether a simple modification of the anesthetic technique and postoperative pain management can improve survival of cancer surgery patients is a highly important question awaiting the results of these prospective trials.

MU OPIOID RECEPTOR ANTAGONISTS

Considering the possibility that morphine might have direct effects on tumor growth, (as opposed to centrally ablating of the stress response), the co-administration of a peripheral antagonist capable of reversing the unwanted peripheral effects of morphine without affecting its central analgesic properties is an attractive option.

This hypothesis has been tested in several experimental settings. An *in vitro* study showed that pre-treatment of cultured human endothelial cells with methylnaltrexone reversed the proliferation- and migration-inducing effects of morphine and other opioid agonists (Singleton et al., 2006). Furthermore, *in vitro* and *in vivo* evidence were documented showing that methylnaltrexone inhibits the disruption of endothelial cell barrier and the increased vascular permeability induced by mu receptor agonists, thrombin or lipopolysaccharide (Singleton et al., 2007). As a result, methylnaltrexone was suggested to have potential therapeutic applications in controlling tumor angiogenesis. Methylnaltrexone was further shown to have synergistic effects on the anti-angiogenic effect of the anti-cancer drugs bevacizumab, 5-fluorouracil, rapamycin, and temsirolimus (Singleton et al., 2008, 2010). Results also demonstrated the involvement of mu opioid receptors in the proliferation and migration of lung cancer cells. Naltrexone as well as MOR knockdown attenuated tumor cell growth and invasion and prevented tumor growth and invasion *in vitro* and metastasis in mice. Interestingly tumors did not develop in MOR knockout mice to which lung tumor cells where injected (Mathew et al., 2011). Moreover, the opioid antagonist naloxone decreased 17beta-estradiol-induced proliferation of MCF-7 breast cancer cells by 65%, due to antagonism of either Mu opioid or estrogen receptors (Farooqui et al., 2006). Currently, a phase II clinical trial is recruiting subjects to study the possible anti-tumor effects of naltrexone tablets, on estrogen-dependent breast cancer (clinicaltrials.gov using the search words opioid antagonist cancer). However, a retrospective clinical study of patients under methadone maintenance therapy failed to show any advantage of naltrexone compared to methadone in the formation of new cancers (Singleton and Moss, 2010).

The potential use of opioid antagonists in the context of cancer is debatable in view of contrasting literature: naltrexone was shown to increase the proliferation of colon, pancreatic, and head and neck cancer cells *in vitro*. This effect was suggested to be due to antagonism of the growth inhibiting effect of endogenous opioid [Met5]enkephalin (Zagon et al., 1996, 2000). Moreover, in a chorioallantoic membrane assay, anti-angiogenic effects of up to 50% were observed for naltrexone (Blebea et al., 2000). Accordingly, a study on angiogenesis during cholestasis in rats showed naltrexone to promote angiogenesis in the liver tissue (Faramarzi et al., 2009). Further studies, including randomized controlled clinical trials, would shed light on whether peripheral opioid antagonists improve cancer free survival when added to opioid analgesia after cancer surgery.

ALTERNATIVE ANALGESIC INTERVENTIONS

Alternative pain-relieving drugs devoid of immunosuppressive effect have been proposed to replace morphine in the postoperative pain management of cancer surgery patients. These include other opioids than morphine, non-steroidal anti-inflammatory drugs (NSAIDs), and adrenergic-active drugs.

Fentanyl and its derivatives sufentanil and remifentanil are highly lipophilic and potent mu receptor agonists, widely used in anesthesia (Forget and De Kock, 2009). While some studies show that these drugs lack the immunosuppressive effects of morphine (Bilfinger et al., 1998; Yeager et al., 2002; Akural et al., 2004), several lines of evidence denoted suppressed cellular immune function and increased risk of metastasis with their perioperative administration (Beilin et al., 1996; Sacerdote et al., 2001; Shavit et al., 2004). Partial agonists such as buprenorphine have been suggested

Table 2 | The effect of perioperative anesthetic/analgesic technique on cancer recurrence and survival.

Type of study	Surgical procedure	Anesthetic/analgesic regimen	Effect on the course of cancer	Reference
Retrospective clinical study	Mastectomy for primary breast cancer	GA + PVA ($n = 50$) GA + PCA ($n = 79$)	Lower cancer recurrence or metastases in patients receiving PVA + GA	Exadaktylos et al. (2006)
Retrospective clinical study	Open radical prostatectomy for invasive prostate cancer	GA + EA ($n = 102$) GA + Opioid analgesia ($n = 123$)	Lower risk of biochemical cancer recurrence in patients receiving EA	Biki et al. (2008)
Retrospective clinical study	Resection of colon cancer	GA + IV opioids ($n = 92$) GA + EA ($n = 85$)	Higher survival rate in patients with non-metastatic, but not metastatic colon cancer	Christopherson et al. (2008)
Secondary analysis of subjects of a randomized controlled clinical trial	Radical prostatectomy for prostate cancer	GA + EA ($n = 49$) GA + IV morphine ($n = 50$)	No difference between the group receiving epidural anesthesia and control groups	Tsui et al. (2010)
Retrospective clinical study	Colorectal cancer surgery	GA + EA ($n = 256$) GA ($n = 253$)	No difference in cancer recurrence rate in normal subjects Lower cancer recurrence rate with EA in subjects older than 64 year	Gottschalk et al. (2010a)
Retrospective clinical study	Brachytherapy for cervical cancer	Neuraxial anesthesia (SA/EA) ($n = 63$) GA ($n = 69$)	No difference in tumor recurrence and mortality rate between the two groups	Ismail et al. (2010)
Prospective, randomized, controlled clinical trial	Excision of cancer by major abdominal surgery such as esophagectomy, gastrectomy, hepatectomy, pancreatectomy, colectomy, nephrectomy, cystectomy, radical hysterectomy, and open prostatectomy	GA + EA ($n = 230$) GA + IV opioids ($n = 216$)	No difference in long-term cancer recurrence and mortality after major abdominal surgery	Myles et al. (2011)
Retrospective Clinical study	Primary excision of cutaneous melanoma	Local anesthesia ($n = 2185$) GA ($n = 2136$)	Slightly increased risk of mortality in patients receiving general anesthesia compared to local anesthesia	Schlagenhauff et al. (2000)
In vitro	Mastectomy for breast cancer patients	GA + PVA ($n = 15$) GA + opioid analgesia ($n = 15$)	Reduced surgical stress response with PVA No difference in pro-angiogenic factors VEGF and PGE2	O'Riain et al. (2005)
In vitro	Breast cancer surgery	Propofol/PVA ($n = 11$) GA + opioid analgesia ($n = 11$)	Serum from patients receiving propofol/PVA inhibited proliferation, but not migration, of breast cancer cells *in vitro*	Deegan et al. (2009)
In vitro	Primary breast cancer surgery	Propofol/PVA ($n = 15$) GA + opioid analgesia ($n = 17$)	Propofol/PVA alters some but not all cytokines and MMPs in favor of resistance against cancer progression and metastasis	Deegan et al. (2010)
In vitro	Primary breast cancer surgery	Propofol/PVA ($n = 20$) GA + morphine analgesia ($n = 20$)	Decreased postoperative serum concentrations of VEGF-C and increased TGF-β in patients receiving propofol/PVA	Looney et al. (2010)

GA, general anesthesia; PVA, paravertebral anesthesia; PCA, patient-controlled analgesia; EA, epidural anesthesia, SA, spinal anesthesia.

as a replacement for morphine and fentanyl, based on animal data showing buprenorphine is devoid of immunosuppressive effects and protects against surgery-induced increased metastasis (Franchi et al., 2007). Tramadol is a low-affinity mu opioid receptor agonist with complementary central inhibition of serotonin and noradrenaline reuptake (Leppert, 2009). Tramadol not only improved immune function in animals (Sacerdote et al., 1999; Tsai and Won, 2001) but also reduced postoperative immunosuppression in patients undergoing surgery for uterine carcinoma, while providing analgesic efficacy comparable to that of morphine (Vickers and Paravicini, 1995; Stamer et al., 1997; Hopkins et al., 1998; Sacerdote et al., 2000; Hadi et al., 2006).

Non-steroidal anti-inflammatory drugs administration has different side effects and considerably lower risk of tolerance than morphine (Anonymous, 1991). NSAIDs with different modes of administration have significant opioid-sparing effects and improve post-surgical pain in different types of surgery. In minor and intermediate surgical procedures they could be considered as alternatives to opioids (Cashman et al., 1985; Anonymous, 1991; Murphy, 1993). NSAIDs further help to improve immune function and host defense against malignant cells (Forget et al., 2010). In addition, because cyclooxygenases (COX) I and II, catalyze the formation of prostaglandins, which are involved in tumor formation, growth, angiogenesis and invasion, NSAIDs and COX inhibitors, particularly COX-2 inhibitors, offer a potential benefit in cancer therapy (Méric et al., 2006). It was demonstrated that adding celecoxib, a selective COX-2 inhibitor, to morphine, reduces the morphine-induced increase in prostaglandin secretion and angiogenesis, growth and metastasis of breast tumor in rodents (Farooqui et al., 2007; Benish et al., 2008). In a murine model of surgery-induced cellular immunosuppression, perioperative administration of the injectable NSAID ketorolac protected, while morphine decreased, the natural killer (NK) cell activity after laparotomy (Colacchio et al., 1994). In a recent retrospective analysis of breast cancer surgery patients, preoperative administration of ketorolac was shown to be associated with lower cancer recurrence while other drugs, namely sufentanil, ketamine, and clonidine, failed to show such beneficial effect (Forget et al., 2010).

Other strategies to assist in controlling postoperative pain and reduce the need for opioid analgesics include systemic administration of glucocorticoids (Salerno and Hermann, 2006; Romundstad and Stubhaug, 2007; Dahl et al., 2010), local infiltration of anesthetics such as lidocaine which was moderately and transiently beneficial in controlling acute pain after abdominal surgery (Dahl et al., 2010), or beta blockers which via catecholamine inhibition may enhance the immune function and prevent cancer progression (Palm et al., 2006). Several studies have shown that intraoperative infusion of beta blockers, and particularly the β1-blocker, esmolol, decreases the intra- and post-operative use of opioids (Johansen et al., 1998; White et al., 2003; Chia et al., 2004; Collard et al., 2007). Moreover, beta blockers have synergistic effects with COX-2 inhibitors, preserving the immune function after surgery, and reducing the risk of postoperative metastasis in rats (Benish et al., 2008). However safety studies, particularly in patients susceptible to risks associated with hypotension, are required (Yu et al., 2011). Currently a randomized clinical trial is testing the ability of intravenous esmolol to enhance postoperative pain relief and reduce the need for intraoperative opioids in patients undergoing laparoscopic prostatectomy and upper gastrointestinal surgery (clinicaltrials.gov using the search words beta-blocker cancer surgery).

Another intervention on the adrenergic system with possible opioid-sparing effect would be α-2 adrenergic receptor activation. The antihypertensive drug clonidine is used preoperatively to prolong regional anesthesia and reduces the need for systemic anesthetics and postoperative opioid analgesics (Pyati and Gan, 2007). However due to its multiple side effects such as excessive hypotension, sedation, and bradycardia its use is limited to regional administration (Buvanendran and Kroin, 2009). Moreover, clonidine and dexmedetomidine, another α2-agonist used in the intensive care unit, were shown to enhance breast tumor growth in a mouse model, possibly via enhanced breast tumor cell proliferation and apoptosis inhibition (Bruzzone et al., 2008).

The anti-convulsant drug gabapentin has also been proposed to reduce acute postoperative pain and the need for opioid administration. This beneficial effect of gabapentin has been confirmed by several randomized controlled clinical trials in oncological and non-oncological surgeries (Eckhardt et al., 2000; Dirks et al., 2002; Fassoulaki et al., 2002; Mathiesen et al., 2007). Pregabalin, another derivative of this family has also been suggested to have opioid-sparing effects, however the results of clinical trials on its dose-dependent efficacy are inconsistent and its use in perioperative pain management still questionable (Dahl et al., 2010). While these drugs are proven to alleviate pain immediately after surgery, the long-term outcome of their administration is unknown (Tiippana et al., 2007). Moreover, although they significantly reduce the postoperative side effects of opioids such as nausea, vomiting, and urinary retention, they aggravate sedation to a great extent (Tiippana et al., 2007; Dahl et al., 2010).

In conclusion, laboratory data available at the moment do not draw a clear picture of morphine as a tumor-promoting or inhibiting agent. The first prospective trial testing whether regional anesthesia and analgesia improved cancer recurrence and metastasis has not confirmed the promising conclusions drawn from retrospective studies, however further prospective trials are still ongoing as the effect may be cancer type specific. Even if these prospective trials were to show a benefit to cancer patients in using regional analgesia and anesthesia and reduced opioid postoperative analgesia, the role of opioids *per se* would not be demonstrated.

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