Review Article

Perioperative analgesia and its influence on cancer outcomes

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Abstract: Cancer is a major cause of morbidity and mortality worldwide. Around two-thirds of those with solid tumors will require surgery as part of their treatment, and there is evidence that perioperative events may influence both short and longer-term outcomes. This may be linked to the creation of an environment that promotes cancer cell growth and potentially propagation of metastases, through the surgical stress response, seeding of cancer cells, and the anesthetic and analgesic drugs used. Given that our practice as anesthetists could influence patient outcomes, it is important to review all aspects of our care. Here we present a summary of the most up to date literature on the influence of perioperative analgesia on cancer outcomes, including *in vitro*, *in vivo* and clinical studies, and the subsequent implications for anesthetic practice. Laboratory data suggests that there could be a significant impact from systemic and regional analgesic drugs and techniques. However, most of the human research is either retrospective or involves systematic reviews and meta-analyses of studies whose primary outcomes were not to study cancer recurrence, and are therefore inconclusive with respect to this. In order for our clinical practice to change, further prospective randomized controlled trials (RCTs) are required to look at the effects of these agents during the perioperative period for a wide range of cancers.

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Introduction

Surgery remains the cornerstone of treatment for patients with solid tumors. Despite surgical resection with a curative intent and the use of increasingly effective (neo)adjuvant therapies, metastatic disease remains common and carries a high risk of mortality. The combination of: inadvertent seeding of cancer cells perioperatively; the physiological disturbances related to the surgical stress response; and the pharmacological effects of certain anesthetic drugs, may promote disease recurrence or the progression of metastatic disease (1).

Pathophysiology of cancer recurrence

There are multiple potential mechanisms by which recurrence or metastases may occur during cancer surgery.

- Local recurrence following proliferation of residual cancer cells;
- Lymph node spread of cancer cells—may occur prior to or during surgery;
- Cavity and distant spread due to seeding of cancer cells during the surgery.

This seeding may be compounded by the effects of the surgery itself, including inflammation, tissue

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hypoxia, angiogenesis, surgical stress response, and immunosuppression. Such effects can disrupt the microenvironment surrounding the tumor and promote both spread and proliferation (2). In addition, surgical techniques and the direct effects of anesthetic and analgesic agents may modulate this shift towards metastasis (3).

Surgery, pain and the stress response

Innate and acquired immune responses are key in the body's response to cancer cells, particularly the anti-tumor activity of the natural killer (NK) cells and CD8 T-cells. Surgery itself is associated with an initial pro-inflammatory state followed by a period of immunosuppression. This is in part caused by the surgical stress response with activation of the sympathetic nervous system and the Hypothalamic-pituitary-adrenal (HPA) axis, as well as the release of inflammatory mediators. Other factors may include hypothermia, allogenic blood transfusion and anesthetic/analgesic agents (2). Activation of the HPA axis stimulates the release of cortisol and catecholamines, these humoral factors not only inhibit the proliferation and anti-tumor activity of NK cells and CD8 T-cells, but also promote the proliferation of regulatory T-cells and Type 2 helper T-cells, which have pro-tumor effects. (1) As their release is stimulated by a combination of tissue trauma and pain, it is suggestive that analgesic techniques could influence or mitigate the effects.

Impact of analgesic techniques

Systemic analgesic agents

Opioids

Opioids make up a large part of anesthetic practice, particularly in cancer surgery, due to their synergistic anesthetic and potent analgesic effects.

The potential effects of opioids on cancer recurrence are variable and, with the evidence available providing conflicting results, it is difficult to identify specific mechanisms. They appear to have both direct and indirect effects on immune function. They may act directly either via opioid receptors [particularly Mu-opioid receptor (MOR)] or non-opioid receptors expressed by immune cells such as NK cells (4,5). Indirect actions occur both via inhibition of NK cytotoxicity through amine release (4), and through activation of the HPA-axis with subsequent glucocorticoid release and immunosuppression (6).

Animal models have shown that over-expression of MOR promotes tumor growth and metastases. MOR expression is increased in several lines of human cancer cells, with an association between this expression and progression of the tumor in an *in vitro* study of lung cancer (7). Their subsequent studies suggested a possible direct effect of MOR on opioid and growth factor-signaling and consequent proliferation, migration and epithelial mesenchymal transition during lung cancer progression (8). This negative impact however is not universal, with some small studies indicating that morphine may have potentially beneficial effects (9,10). Additionally, the impact of different opioids appears to be variable, with buprenorphine (a partial MOR agonist) preventing depression in NK cytotoxicity (6) and tramadol having a potentially immune stimulating effect by enhancing NK cytotoxicity in rats (11).

We must also consider that effective analgesia is an important part of perioperative management, not least because of evidence that pain management may reduce the effect of surgery-induced impairment in the hosts' resistance to metastases. Animal studies have shown that the immunosuppressive effect of fentanyl was only demonstrated in rats that had not been operated on, there was no detrimental effect in those who had surgery, i.e., where the fentanyl's analgesic effect would have been more important (12).

A retrospective clinical study of 900 patients undergoing operations for non-small cell lung cancer (NSCLC) found that high doses of intra-operative fentanyl (median fentanyl equivalent dose 10.15 mcg/kg) were associated with reduced overall survival in stage 1 patients, though appeared to make no difference in stage 2 or 3 (13). However, a large retrospective study of nearly 1,700 patients with colorectal cancer found that intra-operative fentanyl (median dose 3 mcg/kg) had no impact on disease-free or overall survival rates (14). Two retrospective studies of patients undergoing surgery for esophageal squamous cell carcinoma demonstrated conflicting results, with high-dose opioid treatment being strongly associated with disease recurrence in the Korean study, while the US study found improved recurrence-free and overall survival (15,16). In 2018 a systematic review was conducted that looked into the impact of long-term and perioperative opioid use in colorectal cancer, but they found that the 13 studies identified were too heterogeneous to allow for quantitative meta-analysis (17). Remifentanil has been studied within its role as part of total intravenous anesthesia (TIVA), often in comparison with volatile techniques, but there appears to be little evidence

at present concerning its role as an intraoperative analgesic and the potential impact on cancer outcomes. This could be a potential area for further research given the increasing use of TIVA.

Given such variable data it is difficult to make unequivocal recommendations on opioid use in cancer. The evidence may suggest that under certain conditions opioids can promote metastases, but effective analgesia and mitigation of the stress response is also a key concern. Without a prospective randomized controlled trial (RCT) looking specifically into the effects of perioperative opioids on cancer recurrence we are unable to draw definitive conclusions about their on-going use (*Table 1*).

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a common component of multi-model analgesia in the perioperative period, and may also be used for their anti-pyretic effect.

Their effects on cancer propagation and recurrence appear to be multi-factorial, though many elements are poorly understood. As discussed previously, cancer recurrence may be related to the surgical stress response, and as such reducing inflammation may mitigate this effect (18). Other proposed "anti-cancer" mechanisms include effects on enzyme activity, transcription factors, cellular signaling and mitochondrial function (19).

Both *in vitro* and *in vivo* animal studies have shown that NSAIDs may impair cancer cell viability, proliferation, and migration, via both COX-dependent and COX-independent mechanisms (20,21). Several clinical studies have found an improved survival in patients undergoing cancer surgery who received NSAIDs. Two retrospective studies found improved disease-free survival and reduced cancer recurrence in patients with breast cancer who received NSAIDs perioperatively (22,23). A small prospective RCT found that perioperative (commenced 5 days prior to surgery) COX-2 inhibitors combined with a β-blocker suppressed multiple cellular and molecular pathways related to metastasis and disease recurrence in early-stage breast cancer (24). A prospective cohort study of 34,000 breast cancer patients found that post diagnostic use of NSAIDs had little or no association with the rate of breast cancer recurrence. However, those exposed to the drugs pre-diagnosis had a reduced rate of breast cancer recurrence (25). Perioperative use of NSAIDs alone was not found to show survival benefit in patients with NSCLC (26) but a small retrospective study did show an improved long-term survival when NSAIDs were combined with dexamethasone in NSCLC (27).

Overall, the evidence suggests the use of perioperative NSAIDs may be beneficial in reducing cancer recurrence, however a recent review indicated the data was too heterogeneous for meta-analysis and concluded the effects were equivocal (2). Further clinical trials are required to provide more definitive evidence.

α-2-adrenoceptor agonists

α-2-adrenoceptor agonists such as clonidine and dexmedetomidine may be used perioperatively for their sedating and analgesic effects. However, their potential influence on cancer recurrence is poorly understood. Dexmedetomidine reduces cellular apoptosis, potentially increasing cancer cell proliferation and migration (28). Additionally, there may be a negative immunomodulatory effect, particularly with dexmedetomidine (29).

Laboratory and clinical evidence into their effects on cancer recurrence is extremely limited. *In vitro* studies found that dexmedetomidine impaired T-cell cytotoxicity and proliferation (29), as well as promoting cancer cell survival through α-2-adrenoceptor agonism in lung carcinoma and neuroglioma cells (28). Animal models have shown a dose-dependent increase in tumor-cell retention and metastases in those with breast, lung and colon cancer that were given dexmedetomidine (30). Other mouse models demonstrated this effect with both dexmedetomidine and clonidine in breast cancer, where there are known α-2-adrenoreceptors, with α-2-antagonists potentially having an "anti-cancer" effect (31).

A retrospective study of patients with NSCLC demonstrated no difference in recurrence-free survival in those given dexmedetomidine, but a worsening in overall survival rates (32). However, another retrospective study looking at perioperative clonidine in those following surgery for breast or lung cancer found no difference in recurrence-free or overall survival (33). Additionally, a small prospective study found perioperative dexmedetomidine reduced catecholamine release and inflammatory response and had an immunoprotective effect in those undergoing radical gastrectomy (34). It is also worth considering that the use of these analgesic adjuncts may allow for a reduction in potentially harmful volatile agents and systemic opioids, which may have a beneficial effect. Overall, the evidence is insufficient to influence clinical practice at this stage, and prospective RCTs are required.

Table 1 Summary of current evidence and potential areas for future research

Analgesic agent	*In vitro* studies	*In vivo* studies	Human/clinical research	Potential future research
Systemic opioids & cancer recurrence	Negative effect—promotes cancer cell proliferation + migration	Mixed Generally negative effect—facilitates cancer spread Some opioids (e.g., Tramadol, Buprenorphine) may promote immune function	Insufficient, mixed; may increase risk of metastases in some tumors	RCT involving multimodal analgesia without opioids to determine effect
NSAIDs & cancer recurrence	Minimal—may impair cancer cell viability/migration	Minimal—may impair cancer cell viability/migration	Variable—mainly looking at breast cancer: some showing positive effect, some no effect	RCT into NSAID use *vs.* none, particularly in breast cancer
α-2-adrenoceptor agonists & cancer recurrence	Minimal—possible negative effect of dexmedetomidine on immune function + promoting cancer cell survival	Minimal—possible increase in metastases with dexmedetomidine + clonidine	Minimal + mixed—some immunoprotective effect, some reduced survival, others no effect	Possibly RCT into use of dexmedetomidine, particularly in breast cancer (known role of α-2-receptors) given its widespread use
Ketamine	Minimal—suppression of pro-inflammatory cytokines and immunomodulatory	Minimal—reduced metastases compared with fentanyl	No data	RCT into multimodal analgesic techniques without opioids on cancer outcomes
IV lidocaine & cancer recurrence	Suggests beneficial effect—reducing risk of cancer cell spread + survival	Limited; suggests reduction in metastatic load	No data	Pilot studies into effect of IV lidocaine infusions ± RCT
Regional analgesia & cancer recurrence	–	Minimal data, suggested no improvement in cancer outcomes	Inadequate data, conflicting results	RCTs in progress assessing regional *vs.* opioid

RCT, randomized controlled trial; NSAID, non-steroidal anti-inflammatory drug; IV, intravenous.

Ketamine

Ketamine is a non-competitive NMDA receptor antagonist that can be used for anesthesia, sedation and analgesia in the perioperative period. There is extremely limited data regarding the impact of perioperative ketamine use on cancer outcomes. The theoretical benefits come from its potential immunomodulatory effects and anti-inflammatory properties (35-37).

In vitro studies have shown that ketamine reduces the production of pro-inflammatory mediators TNF-α, IL-6 and IL-8 in response to Staphylococcal enterotoxaemia in whole blood (38), a response supported by a canine study of induced endotoxemia (37). A small clinical study looked into the inflammatory response following abdominal surgery, and found that pre-induction doses of ketamine (0.15 mcg/kg) reduced levels of TNF-α and IL-6, whilst preserving IL-2 (35). Forget *et al.* [2010] compared the use of ketamine, fentanyl and clonidine in rats undergoing laparotomy, and found that although ketamine reduced NK activity in non-operated animals, the levels were comparable to control post-surgery. Ketamine also reduced the incidence of lung metastases in both operated and non-operated animals (39).

There are no clinical studies into the effect of perioperative ketamine on cancer recurrence and metastases and therefore as yet there are no recommendations for its use for this purpose. Given its anti-inflammatory effect, as well as its potential volatile and opioid sparing properties, it is worth exploring in prospective RCTs.

Local and regional anesthesia

Local anesthetic (LA) agents

Amide LAs themselves seem to be protective against tumor growth and metastasis. The exact mechanism is unclear but lidocaine has been shown to reduce levels of the inflammatory markers IL-1, TNF-α and IL-8, in addition to direct effects on cancer cells (40,41). These may be via blockade of voltage-gated sodium channels, or other mechanisms such as: direct cytotoxicity and induction of apoptosis; inhibition of proliferation, migration, and invasion; and modulation of gene expression via methylation (42).

The evidence supporting this effect mainly comes from *in vitro* studies and there is very little clinical evidence at present. *In vitro* studies of bupivacaine demonstrated that it has direct 'anti-cancer' properties at clinically relevant concentrations through activation of the intrinsic apoptotic pathway in prostate cancer, and both the extrinsic and intrinsic pathways in ovarian cancer (43). A study of ropivacaine demonstrated inhibition of metastatic colon cancer cell lines with similar potency to its sodium channel inhibition (44). Lidocaine has been found to reduce cell viability, inhibit tumor cell migration and compromised cell growth in laboratory studies. *In vivo* studies have demonstrated improved survival (45) and reduced metastatic load when used in conjunction with volatile anesthesia (3) in mouse models of breast cancer.

The effects of regional local anesthesia are discussed below, but with regards to intravenous (IV) lidocaine infusions there are no significant clinical trials that have investigated its benefit specifically.

Regional anesthesia and analgesia

The effect of regional anesthesia on the incidence of metastases and cancer recurrence is unclear. The potential benefits include: the direct effects of LA agents (discussed above); attenuation of the stress response to surgery through either provision of effective analgesia or sympathetic nervous system blockade; reducing opioid requirements and thus their potential negative impact; potentially allowing avoidance of volatile anesthesia and its detrimental effects (46).

As with most of the interventions discussed in this article, the evidence into the effect of regional anesthesia on cancer recurrence is variable. There have been a wide range of studies and systematic reviews that have attempted to identify the effects of regional techniques. On a cellular level, a few small studies of breast cancer patients identified greater NK cytotoxicity, improved immune cell infiltration into cancer tissue and increased apoptosis in those receiving a "propofol + paravertebral block" (PPA) technique *vs.* a "sevoflurane + opioid" (GA) technique (47-49). However, an International RCT of over 2,000 women with breast cancer having potentially curative surgery found that the PPA technique was not associated with a reduction in breast cancer recurrence when compared to GA (50). With regards to surgical resection for NSCLC, a retrospective study in Taiwan found that perioperative epidural analgesia did not improve disease free or overall survival rates (51).

One of the most recent meta-analysis from 2017 looked at over 67,500 patients found that regional anesthesia has no overall survival, recurrence-free survival, or biochemical recurrence-free survival benefit (52). A smaller meta-analysis of 3,000 patients from 2014 indicated that epidural + GA may be associated with improved survival in those with

operable prostate cancer when compared to GA alone, but that there was no benefit identified in colorectal cancer (53). A meta-analysis of 10 retrospective studies indicated that while there was no prolongation in biochemical recurrence-free survival after radical prostatectomy there was an improvement in overall survival when regional techniques were used (54). Another meta-analysis showed improvement in overall survival post cancer surgery particularly in colorectal cancer, as well as a reduced risk of cancer recurrence (55). Finally, a meta-analysis of 20 studies published in 2015 suggests that RA may improve overall survival but not reduce cancer recurrence after oncologic surgery (56). The heterogeneity of studies within many of these meta-analyses makes drawing conclusions difficult, and the most recent Cochrane Report [2014] indicates that evidence into regional anesthesia and cancer recurrence is inadequate (46). More prospective RCTs are required.

Conclusions

While there is currently laboratory evidence that certain types of perioperative analgesic techniques may influence cancer outcomes, either positively or negatively, the clinical data is generally lacking. Most of these studies are retrospective, making the exclusion of confounding variables more difficult and bias more likely, Furthermore, the heterogeneity of their methodology and data makes formal meta-analysis difficult. Prospective RCTs are required in order to produce evidence that could significantly influence and alter clinical practice. This in itself presents a huge task, given the wide variety of cancers requiring surgical intervention, all of which have unique properties that preclude mass generalization of results. A number of these trials are currently on going, which should provide more information over the next few years.

Whilst awaiting the outcomes of these trials it is important to note that in the first instance our priorities should be providing a balanced anesthetic with adequate multi-modal analgesia in the perioperative period.

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