Anaesthetic technique and cancer recurrence: current understanding

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Abstract

Introduction

Over the past decade, dozens of studies have been published that examine the effect of anaesthetic technique on cancer recurrence. In this article, we review the literature on the hypothesis that anaesthetic and analgesic techniques may impact long-term outcomes after oncologic surgery. The literature in this review was obtained from queries conducted on Google Scholar, PubMed and MEDLINE. Search terms included 'anaesthesia and cancer', 'IV anaesthetics and cancer', 'volatile anaesthetics and cancer', 'opioids and cancer', 'anaesthesia and tumour metastasis', 'regional anaesthesia and cancer' and 'local anaesthetics and cancer'. Five in vitro, seven animal, five clinical retrospective and two prospective randomised control trials were included in our review.

Conclusion

We may have to consider the conflicting evidence presented before us and adjust our current clinical practice in those oncologic patients where there are sufficient data to support an 'anti-cancer' anaesthetic.

Introduction

Despite advancements in the field of oncology, cancer remains the second most common cause of death in the United States. Cancer accounts for one out of every four deaths with more than 1500 cancer-related deaths occurring each day. In 2012, over 1.6 million new cancer cases were diagnosed in the United States. This estimate does not include skin cancers and patients with carcinoma in situ, which are not reported to national cancer registries. Although cancer can develop at any age, the risk of being diagnosed with cancer increases with age. Projections suggest that well over 75% of cancers are diagnosed in persons aged 55 and older. With the growing geriatric population and the rising incidence of cancer diagnoses, anaesthesiologists have greater opportunities to manage oncology patients in their daily practice.

Over the past decade, dozens of studies have been published that examine the effect of anaesthetic techniques on cancer recurrence. In this article, we review the literature on the hypothesis that anaesthetic and analgesic techniques may impact long-term outcomes after oncologic surgery. The literature in this review was obtained from queries conducted on Google Scholar, PubMed and MEDLINE. Results were limited to the English language. Search terms included 'anaesthesia and cancer', 'IV anaesthetics and cancer', 'volatile anaesthetics and cancer', 'opioids and cancer', 'anaesthesia and tumour metastasis', 'regional anaesthesia and cancer' and 'local anaesthetics and cancer'. Five in vitro, seven animal, five clinical retrospective and two prospective randomised control trials were included in our review.

Discussion

Cancer cell biology

Pathogenesis of tumour metastasis

Cancer begins with the unregulated cell growth of a primary tumour. The mechanism of tumour metastasis encompasses a series of steps that is dependent on the intrinsic properties of tumour cells as well as the response of the host. The process of tumour metastasis includes the initial transformation and proliferation of neoplastic cells. Angiogenesis then ensues secondary to angiogenic factors, including vascular endothelial growth factor (VEGF) and prostaglandin E₂, both released from tumour cells. The neovascularisation occurring from host tissue allows nutrients to flow through these new capillaries, supporting their growth and ensuing proliferation. These tumour cells then penetrate neighbouring normal tissue, entering host circulation via lymphatics and blood vessels. Once in circulation, the aggregate of tumour cells are transported to distant sites, become trapped in capillary beds of distant organs, extravasate into the parenchyma of the organ and the metastatic cells then repeat the proliferative cell cycle.

Immune system response to cancer

It is well recognised that cell-mediated immunity is the initial defence mechanism against invading cancer cells. Cell-mediated immunity is comprised of two types of immune response: the innate and the adaptive immune response. The former is a nonspecific system that does not require prior sensitisation and the latter is antigen-specific immune cell mediated. Both work in conjunction to detect and destroy the presence of tumour cells before it is clinically evident. The major cell components include natural killer (NK) cells, cytotoxic T cells (CTLs), mononuclear cells and dendritic cells. There has been a higher incidence of developing
cancer reported in patients with decreased NK cell activity as well as an association between stress-induced attenuation of NK cell activity and the accentuation of breast tumour growth in rat models. However, some studies have shown a positive association between NK cell activity and a reduced incidence of cancer, a meta-analysis from 2012 suggested that the anaesthetic technique has no clinically significant effect on NK cell function.

Cytotoxic T lymphocytes have also demonstrated an importance in anti-tumour activity. Several studies have reported an association between improved patient morbidity and overall survival in a variety of cancers with accumulation of CTLs within the tumour mass.

**Tumour response to surgery**

Surgery remains the 'gold standard' and primary treatment for patients with solid tumours in conjunction with chemotherapy, radiotherapy and endocrine therapy. Despite optimal surgical debulking, excision of the tumour may not adequately remove the 'minimal residual disease' (MRD). MRD is defined as clinically undetectable cancer cells that remain despite the surgical removal of macroscopic tumour. Several studies have demonstrated that the mechanical act of surgery promotes tumour metastasis through various mechanisms: it disperses tumour cells into circulation; surgical stress response leads to depression of cell-mediated immunity and surgery promotes angiogenesis while attenuating the release of anti-angiogenic factors.

It is believed that the interval between the immediate postoperative period and the initiation of supplemental therapeutic treatment coincides with the MRD metastasis. The balance between the metastatic potential of MRD and the stability of the host immune system potentially determines the metastatic recurrence of tumour following surgery. Consequently, the perioperative period represents the highest risk for neoplastic metastasis during the course of a patient's cancer treatment.

**Effects of general anaesthesia on immune function and cancer**

Although great strides have been made in the areas of endocrine therapy, radiation therapy and chemotherapy, surgical excision of a solid tumour offers the best opportunity for disease-free prognosis. Recent evidence suggests, however, that certain anaesthetic agents used during surgery may contribute to the immunosuppression that can negatively affect postoperative cancer recurrence.

Our knowledge regarding the potential effects of anaesthetic agents on immune function stems from in vitro testing and studies on animal models (Table 1), as well as some human studies (Table 2). Here, we will review the effects of intravenous and inhaled anaesthetic agents on host defences and their implication on postoperative tumour recurrence.

**Intravenous anaesthetic agents**

Experiments on rats inoculated with mammary adenocarcinoma suggest that certain intravenous agents may suppress NK cell activity and promote tumour cell metastasis. Both ketamine and thiopental significantly reduced NK cell activity and increased the number of retained tumour cells found at autopsy. Ketamine had the strongest impact, promoting tumour retention and metastasis more than 2.5-fold. Similar inhibitory effects on NK cell activity were seen in rats given 10 mg/kg ketamine 1 h prior to surgery. Unlike other anaesthetics, propofol was not found to reduce NK cell activity or increase tumour retention.

**Inhaled anaesthetic agents**

Similar to intravenous anaesthetics, impaired lymphocyte function may be responsible for the immunosuppressive effects of volatile anaesthetic agents. In a mice model, both isoflurane and halothane were found to inhibit interferon-induced NK cell induction (>90% and 67%, respectively). Isoflurane and sevoflurane have also been shown to induce apoptosis in human T-lymphocytes in vitro in a dose-dependent manner. In vivo studies on humans can be more difficult to interpret, mainly because of confounding variables and the medications patients are exposed to which may also affect tumour recurrence. Brand et al. looked at patients undergoing general anaesthesia (GA) with fentanyl, thiopental and isoflurane for elective orthopaedic surgery and found a significant decrease of circulating NK cells in peripheral blood. One large retrospective study on over 4000 patients found that GA for primary excision of melanoma was associated with a decrease in survival rate (relative risk 1.46, P < 0.0001). Additionally, volatile anaesthetics may influence cancer progression via effects on tumour cell gene expression. Gene expression profiles can be used for risk assessment, and expression profiles can be used for risk assessment.
stratification, disease classification and prognosis prediction in cancer patients. Gene expression profiling has been shown to predict disease outcome in patients with breast cancer based on clinical and histological criteria. A pilot study in 2010 showed that volatile anaesthetic agents could pave profound time-dependent effects on gene expression in ex-vivo breast and brain tumour cell cultures. Nitrous oxide remains one of the most commonly used agents during GA. However, it is well documented that nitrous oxide exerts numerous immune modulating effects. Via its interaction with vitamin B12 and inactivation of methionine synthase, nitrous oxide impairs DNA and purine synthesis. Impaired DNA synthesis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miao et al.</td>
<td>In vitro</td>
<td>Untreated colon carcinoma cells vs colon carcinoma cells + propofol</td>
<td>Propofol decreased expression of MMP-2 and -9 and decreased carcinoma cell invasive activity</td>
</tr>
<tr>
<td>Xu et al.</td>
<td>In vitro</td>
<td>Untreated oesophageal carcinoma cells (ECA-109) vs. ECA-109 cells + propofol</td>
<td>Propofol significantly promoted cell apoptosis and inhibited proliferation in a dose- and time-dependent manner</td>
</tr>
<tr>
<td>Loop et al.</td>
<td>In vitro</td>
<td>Sevoflurane vs. isoflurane vs. desflurane</td>
<td>Sevoflurane and isoflurane, but not desflurane, induced apoptosis in human T lymphocytes in a dose-dependent manner</td>
</tr>
<tr>
<td>Singleton et al.</td>
<td>In vitro</td>
<td>Morphine alone vs. morphine + methylnaltrexone</td>
<td>Morphine alone induced endothelial cell proliferation and migration, which was inhibited by methylnaltrexone</td>
</tr>
<tr>
<td>Melamed et al.</td>
<td>Animal–mice model</td>
<td>Saline vs. ketamine, thiopental, halothane, or propofol</td>
<td>All anaesthetics, except propofol, reduced NK activity and increased lung tumour retention or metastases</td>
</tr>
<tr>
<td>Forget et al.</td>
<td>Animal–mice model</td>
<td>Sevoflurane + saline vs. sevoflurane + fentanyl, clonidine or ketamine</td>
<td>All agents decreased NK cell activity in nonoperated rats and 24 h postop</td>
</tr>
<tr>
<td>Kushida et al.</td>
<td>Animal–mice model</td>
<td>Intraperitoneal saline vs. intraperitonealpropofol or midasolam</td>
<td>Increased cytotoxic T-lymphocyte activity and reduced tumour growth in propofol group only</td>
</tr>
<tr>
<td>Markovic et al.</td>
<td>Animal–mice model</td>
<td>Halothane vs. isoflurane</td>
<td>Both halothane and isoflurane inhibited interferon stimulation of NK cytotoxicity</td>
</tr>
<tr>
<td>Belin et al.</td>
<td>Animal–mice model</td>
<td>Morphine vs. fentanyl vs. sufentanil</td>
<td>All three drugs significantly suppressed NK cytotoxicity at 3 h after administration</td>
</tr>
<tr>
<td>Farooqui et al.</td>
<td>Animal–mice model</td>
<td>Morphine vs. Celecoxib vs. morphine + Celecoxib</td>
<td>Morphine alone increased angiogenesis, tumour weight and metastasis. Co-administration of Celecoxib prevents these morphine-induced effects</td>
</tr>
<tr>
<td>Harimaya et al.</td>
<td>Animal–mice model</td>
<td>Intraperitoneal saline vs. intraperitoneal morphine</td>
<td>Morphine significantly reduced the number of tumour colonies and the weight of tumour-containing lung</td>
</tr>
<tr>
<td>Page et al.</td>
<td>Animal–mice model</td>
<td>Anaesthesia with vehicle (no surgery) vs. anaesthesia with morphine (no surgery) vs. surgery with vehicle vs. surgery with prop morphine vs. surgery with postop morphine</td>
<td>Surgery resulted in a 2-fold increase in tumour cell retention, which was significantly attenuated by morphine treatment. The preop morphine group exhibited a 65%–70% attenuation of tumour retention vs. only a 50% attenuation in the postop morphine group</td>
</tr>
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limits cell production and may cause bone-marrow depression\textsuperscript{31,33}. Reanalysis of data from a previous randomised, controlled trial initially designed to assess the effect of nitrous oxide on surgical site infection in patients undergoing colectomy showed that patients who received nitrous oxide had no significant difference in cancer recurrence compared with those receiving nitrogen and oxygen ($P = 0.72$)\textsuperscript{34}.

**Opioids**

Opioids are frequently used in the treatment of oncology patients for both acute postoperative pain and chronic pain conditions. Opioid therapy, both acute and chronic, has been shown to have immunomodulating effects. Opioid administration suppresses immune function including NK cell activity, phagocyte function, as well as cytokine and antibody production\textsuperscript{35}. The published literature, however, is conflicting; with some reports suggesting that opioids may either promote or inhibit cancer metastasis\textsuperscript{36}. Similar to other anaesthetic agents, opioids have been found to suppress NK cell cytotoxicity in both rat and human models\textsuperscript{37,38}. It has also been proposed that opioids affect tumour growth by activation of VEGF receptors. Singleton et al.\textsuperscript{39} showed that morphine promoted tumour cell migration and proliferation in vitro in association with VEGF receptor activation and enhanced angiogenesis. Proposed mechanisms to explain the effect of opioids on angiogenesis include upregulation of COX-2 and increased prostaglandin production\textsuperscript{40}.

In contrast to the above results, a beneficial effect for perioperative opioids has been demonstrated in a few studies. In an experimental model of colon cancer, morphine inhibited cancer-promoting MMP production and decreased adhesion and migration of colon cancer cells to extracellular matrix components\textsuperscript{41}. Page et al.\textsuperscript{42} was able to show a reduction in surgery-induced tumour retention in all rats who received morphine; the effect was more pronounced if morphine was administered prior to laparotomy. This may suggest a role for the preoperative use of opioids to attenuate surgery-induced increase in tumour metastasis.

**Effects of regional anaesthesia on immune function and cancer**

There are many conflicting studies regarding regional anaesthesia and its impact on cancer recurrence (Table 2). It has been reported that regional anaesthesia decreases some of the risk factors that promote cancer metastasis by attenuating the neuroendocrine stress response to surgery, reducing pain, the need for GA, minimising opioid use and decreasing pro-inflammatory cytokines\textsuperscript{43}. The theory is that regional anaesthesia may leave an intact immune system which could potentially decrease cancer recurrence via endogenous removal of tumour cell microemboli.

A small retrospective study of patients undergoing mastectomy compared cancer and metastasis-free survival in patients who received GA with paravertebral anaesthesia and analgesia (PVA) or GA with postoperative continuous morphine patient-controlled analgesia (PCA). Patients receiving GA + PVA demonstrated a higher rate ($P = 0.012$) of cancer and metastasis-free survival than GA + morphine PCA\textsuperscript{44}. An animal study of rats undergoing laparotomy demonstrated that the addition of spinal analgesia to GA decreased the incidence of lung metastasis when compared with GA alone\textsuperscript{45}. Another study of patients having prostate cancer surgery showed that patients who had GA + epidural analgesia had a lower risk of biochemical cancer recurrence than patients with GA + intravenous opioids\textsuperscript{46}.

On the other hand, a small retrospective study observed that men who underwent radical prostatectomy demonstrated no difference in disease-free survival between GA and combined general and epidural anaesthesia\textsuperscript{47}. A large analysis of 42,000 patients with colon cancer who underwent colon resection demonstrated that epidural use was associated with 5-year improved overall survival, but not actual cancer recurrence\textsuperscript{48}. Another retrospective study of patients with colorectal cancer who had laparoscopic surgery illustrated no effect of spinal or epidural analgesia compared with intravenous opioid analgesia\textsuperscript{49}.

As of 2013, the only long-term study published was the multicentre prospective randomised-control clinical trial, known as the MASTER trial. This prospective clinical analysis compared patients who underwent major abdominal surgery. They were randomised to receive GA with either opioid or epidural analgesia and no significant difference was found in cancer-free survival between the groups. A potential variable that may represent a confounding factor in this study is that the amount of volatile anaesthetic used was not recorded during data collection\textsuperscript{50}. There are other smaller prospective studies but they also suffer from various confounders such as the use of multimodal anaesthesia and the inability to determine whether regional anaesthesia impacts cancer recurrence. To date, many of the common cancers offer potential areas for future research (Table 3).

**Conclusion**

The role of endogenous cellular immunity in the defence against cancer metastasis and recurrence is well established. Both animal and human studies suggest that NK cell activity may play a critical role in determining disease-free survival after oncologic surgery. Other components of our immune system also contribute to host protection. The possible interaction between anaesthetic technique, cellular immunity and cancer recurrence has been studied over the years. Some, but not all, evidence...
suggest that anaesthetic technique may impact cancer recurrence rates. However, more prospective randomised controlled clinical trials are necessary to statistically demonstrate a causal relationship. There are several ongoing clinical trials by Outcomes Research Consortium in Cleveland, Ohio comparing an ‘anti-cancer’ anaesthetic technique utilising a propofol-based anaesthetic with regional anaesthesia on primary cancer patients versus standard GA with opioid analgesia; these investigations will require several more years until completion. While we anxiously await the results, we may have to consider the conflicting evidence presented before us and adjust our current clinical practice in those oncologic patients where

**Table 2 Clinical evidence on effects of regional anaesthesia and cancer recurrence**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Reference</th>
<th>Surgery</th>
<th>Anaesthetic technique</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>Exadaktylos et al.</td>
<td>Mastectomy and lymph node dissection</td>
<td>GA + PVB (n = 50) GA + opioid analgesia (n = 79)</td>
<td>4-fold decrease in cancer recurrence in PVB group at 4 year follow-up</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Biki et al.</td>
<td>Radical prostatectomy</td>
<td>GA + TE (n = 102) GA + opioid analgesia (n = 123)</td>
<td>57% reduction in cancer recurrence in TE group P = 0.012</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Gottschalk et al.</td>
<td>Open colectomy</td>
<td>GA + epidural (n = 256) GA + opioid analgesia (n = 253)</td>
<td>No difference in cancer recurrence at 1-year follow-up</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Day et al.</td>
<td>Laparoscopic colorectal resection</td>
<td>Epidural (n = 7) Spinal (n = 144) Morphine PCA (n = 173)</td>
<td>No difference in recurrence or survival at 5-year follow-up</td>
</tr>
<tr>
<td>RCT</td>
<td>Tsui et al.</td>
<td>Radical prostatectomy</td>
<td>GA + epidural (n = 49) GA + opioid analgesia (n = 50)</td>
<td>No difference in survival at 4.5-year follow-up</td>
</tr>
<tr>
<td>RCT</td>
<td>Myles et al.</td>
<td>Abdominal surgery</td>
<td>GA + epidural (n = 230) GA + opioid analgesia (n = 216)</td>
<td>No difference in recurrence or survival at 5 year follow-up</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Cummings et al.</td>
<td>Open colectomy</td>
<td>Epidural (n = 9670) Opioid analgesia (n = 32,481)</td>
<td>61% survival with epidural at 5 year follow-up vs.55% with opioid P &lt; 0.001; no difference in cancer recurrence</td>
</tr>
</tbody>
</table>

PVB, paravertebral block; TE, thoracic epidural; RCT, randomised controlled trial; GA, general anaesthesia; PCA, patient-controlled analgesia.

**Table 3 Proposed areas of future research**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Sex</th>
<th>Peak age</th>
<th>Ethnicity</th>
<th>Affected area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Osteosarcoma</td>
<td>More common in men</td>
<td>10–30 years</td>
<td>Common in Blacks (6.8 million/year) and Hispanics (6.5 mil/year)</td>
<td>Metaphyseal region of tubular long bones</td>
</tr>
<tr>
<td>• Ewing Sarcoma</td>
<td>More common in men</td>
<td>10–20 years</td>
<td>Common in Caucasians</td>
<td>Pelvis, proximal long tubular bones (growth plates)</td>
</tr>
<tr>
<td>Gynaecology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cervical</td>
<td>Women</td>
<td>40–50 years</td>
<td>Common in Hispanics and Blacks</td>
<td>Cervix</td>
</tr>
<tr>
<td>• Endometrial</td>
<td>Women</td>
<td>55–65 years</td>
<td>Common in Whites</td>
<td>Uterus</td>
</tr>
<tr>
<td>Orthopaedic tumours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chondrosarcoma</td>
<td>Men = women</td>
<td>50–70 years</td>
<td>Caucasians</td>
<td>Pelvis, proximal/distal femur, proximalhumerus, ribs</td>
</tr>
<tr>
<td>• Giant cell tumour</td>
<td>Women</td>
<td>20–40 years</td>
<td>Asians</td>
<td>Periarticular long bones of extremities</td>
</tr>
<tr>
<td>• Fibrosarcoma</td>
<td>Men</td>
<td>40–70 years</td>
<td>Blacks</td>
<td>Knee, hip and shoulder regions, pelvis</td>
</tr>
</tbody>
</table>
there are sufficient data to support an ‘anti-cancer’ anaesthetic.

**Abbreviations list**

CTLs, cytotoxic T cells; GA, general anaesthesia; MMPs, matrix metalloproteinases; MRD, minimal residual disease; NK, natural killer; PCA, patient-controlled analgesia; PVA, paravertebral anaesthesia and analgesia; VEGF, vascular endothelial growth factor.

**References**


