Anesthesia and cancer recurrence: What is the evidence?

Surgery forms a major component of the multimodality treatment of solid tumors. Primary excision may be curative by itself, or it may be combined with neoadjuvant or adjuvant chemotherapy and/or radiotherapy. Despite advances in therapy, loco-regional recurrence and metastases remain a major source of morbidity and mortality in cancer patients. There has been increasing interest in the events occurring during surgery and in the perioperative period that lead to liberation of cancer cells into the circulation and enable survival and growth of circulating tumor cells, leading to regional recurrences and metastases. Data from laboratory and animal experiments suggests that anesthesia and anesthetics may contribute significantly to this pro-tumor environment and affect long-term outcomes after cancer surgery. The review article published in this issue of the journal,[1] summarizes the experimental data and raises a valid concern regarding the potential role of anesthetic and analgesic techniques in causing cancer recurrence and metastases. The authors conclude that perioperative care has a definitive role in cancer-free survival and suggest modifying our current practice.[1] Does this mean that anesthesiologists have at least been partly responsible (unknowingly and unwittingly) for poor oncological outcomes? We suggest that we should also examine the available human clinical data in greater detail and perhaps be more circumspect in our conclusions at this stage.

What is the Experimental Evidence?

Several reviews, including the article published in this issue of the journal, have dealt with this subject.[1-6] We will briefly summarize the major conclusions.

At least three factors operating in the perioperative period lead to a shift in the balance toward tumor progression.

1. Surgery itself and the associated neuroendocrine stress response have a negative effect on the immune system due to depressed cell-mediated immunity. Even after complete excision of the tumor, circulating tumor cells released during the surgical procedure may eventually lead to recurrence or metastases as they escape the immune surveillance.[7] Concentrations of tumor-related anti-angiogenic factors (e.g., angiostatin and endostatin) are decreased while angiogenic factors such as vascular endothelial growth factor (VEGF) are increased. Surgery is also associated with release of transforming growth factor-beta (TGF-B) that plays a significant role in establishing tumor blood supply and cell proliferation.[8-10]
2. Anesthesia impairs numerous immune functions, including those of neutrophils, macrophages, dendritic cells, T-cell, and natural killer (NK) cells. Induction agents (ketamine, thiopentone) as well as inhalation agents (halothane) have been shown to depress NK cell activity in animal studies. Upregulation of hypoxia-inducible-factors (HIF) in tumor cells by volatile anesthetics may contribute to a tumor's recurrence by stimulating cytoprotective or protumorigenic behavior in residual cells.[5] Propofol may not contribute to the depression of immune function according to current available evidence.[11] Propofol also does not upregulate synthesis of HIF.[5] Amide local anesthetics have shown *in vitro* studies to have cytotoxic activity, which could prove to be beneficial in preventing cancer recurrence.[12]
3. Opioid analgesics inhibit both cellular and humoral immune function in humans, increase angiogenesis, and promote breast tumor growth in rodents. Opioids interfere with immune function by depressing NK cell activity.[4,5] However, opioids may reduce the stress response to pain and offer some benefit.

Perhaps regional anesthesia might play an important role in preventing cancer recurrence and metastases, both by attenuating the stress response to surgery and pain, and also by providing excellent analgesia that will minimize or eliminate the need for opioids.

The data from animal models, cell lines, and experimental laboratory data in humans thus points to a significant role for perioperative anesthetic care in the outcomes from cancer.

What is the Human Clinical Data on Anesthesia and Cancer Outcomes?

There are no results from prospective randomized controlled trials yet available. Human clinical data consists largely of retrospective reviews. The best available evidence is in the form of post-hoc analyses of randomized controlled trials (RCTs) that were originally designed to answer a different question.

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The studies essentially compared patients given general anesthesia (GA) and/or regional anesthesia plus regional analgesia versus patients given GA and systemic analgesia. They are summarized below:

Breast cancer

In a retrospective study, 129 patients received GA for surgery for breast cancer.[13] Patients who received paravertebral block for analgesia had nearly 4 times greater recurrence-free survival (RFS) compared to those who received intravenous patient controlled analgesia (PCA) (6% vs. 24%, $P = 0.013$).

Gastrointestinal cancers

Two retrospective studies showed benefit in some groups of patients, but not in all patients. Gupta *et al.*[14] found that patients with colon cancer did not have a better survival with epidural analgesia, whereas patients with rectal cancer did. Christopherson[15] found no difference in overall survival (OS) in patients with colon cancer receiving general anesthesia (GA) compared with epidural plus GA. However, epidural use was associated with better survival in patients without metastases upto 1.46 years after surgery. Gottschalk *et al.*[16] reviewed the records of 669 patients undergoing colorectal cancer surgery. They concluded that use of epidural analgesia for perioperative pain control during colorectal cancer surgery was not associated with a decreased cancer recurrence; however, a potential benefit was observed in older patients.

Two retrospective studies and two studies performing secondary analyses from previous prospective RCTs showed no benefit of regional versus GA. The Surveillance, Epidemiology, and End Results (SEER) study[17] was a large, population-based study of over 40,377 patients. Outcomes of patients undergoing surgery for colon cancer receiving epidural analgesia were compared to those receiving traditional analgesia. The type of postoperative analgesia in the non-epidural group was not clear. There was no difference in RFS survival, but a significant benefit on OS with epidural analgesia. Day *et al.*[18] performed a retrospective analysis of 424 patients from a prospectively maintained database of patients undergoing laparoscopic resection for colorectal adenocarcinoma. There was no OS or disease-free survival (DFS) advantage with the use of regional analgesia (spinal or epidural) in patients undergoing laparoscopic colorectal cancer resection. No survival advantage was seen with regional analgesia even when patients with extranodal metastases were removed from the analysis.

Myles *et al.* performed a post-hoc analysis of patients in the MASTER trial who had potentially curative resection of cancer.[19] The MASTER trial[20] was a prospective RCT comparing combined epidural and GA versus GA plus systemic opioid analgesia for major abdominal surgery. Of the 503 patients studied, most of whom had colon cancer, RFS was similar in both epidural and control groups (hazard ratio 0.95, 95% confidence interval 0.76 to 1.17; $P = 0.61$). They concluded that use of epidural block in abdominal surgery for cancer is not associated with improved cancer-free survival.[19] Similarly, Binzack *et al.*[21] performed a retrospective study of patients previously included in a prospective RCT. The EP group received GA with bupivacaine thoracic epidural analgesia, and the SC group received GA with fentanyl followed by continuous subcutaneous morphine. After 5 years, RFS was 43% in EP group and 24% in SC group, but the difference did not reach statistical significance for RFS nor for overall survival ($P = 0.10$ and 0.16, respectively). The type of analgesia was not a statistically significant predictive factor for RFS on multivariate analysis.

The only study to suggest a worse outcome with epidural anesthesia was a retrospective study in patients undergoing radiofrequency ablation of hepatocellular carcinoma under GA or epidural anesthesia.[22] In the multivariate analysis, the intraoperative and postoperative use of opioids was not associated with worse outcomes. The authors speculated that longer and more frequent treatments were possible under GA, contributing to the better outcome observed.

Ovarian cancer

Two of four retrospective studies demonstrate a benefit with intraoperative use of epidural anesthesia and postoperative analgesia compared to GA followed by intravenous analgesia.[23,24] In two other studies, epidural anesthesia and analgesia were not associated with better RFS or OS compared to non-epidural analgesia.[25,26]

Prostate cancer

The results of three retrospective studies conducted in patients with prostate cancer are also conflicting. Biki *et al.*[27] showed a significant 57% difference in biochemical RFS in 102 patients who received combined general and epidural anesthesia and analgesia compared with 123 patients who received GA and parenteral opioids. Wuethrich *et al.*[28] found significant clinical PFS, but not biochemical RFS, cancer-specific survival, or OS. Forget, in a large study of 1111 patients, was unable to show a difference in biochemical RFS.[29] Tsui *et al.*[30] performed a secondary analysis of subjects undergoing radical prostatectomy who had participated previously in a RCT evaluating pain control, blood loss, and the need for perioperative allogeneic blood transfusion. The patients were randomly allocated to receive either GA alone ($n = 50$) or combined general and epidural anesthesia ($n = 49$). No difference was observed between the epidural and control groups in disease-free survival at a median follow-up time of 4.5 years.

Malignant melanoma

In one retrospective study, there was no difference in survival between patients receiving general and spinal anesthesia compared to those receiving GA alone.[31] Another study of 4329 patients found a statistically significant improvement in probability of survival (85% vs. 78%) in patients given local anesthesia as opposed to general anesthesia for excision of melanoma.[32]

Chen and Miao performed a meta-analysis[33] that included 14 studies and 18 sub-studies. They found that epidural anesthesia and/or analgesia might be associated with improved overall survival in patients with operable cancer undergoing surgery (especially in colorectal cancer), but it did not support an association between epidural anesthesia and cancer control, as there was no difference in the recurrence-free survival.

In summary, the results from retrospective studies are conflicting. Many studies could not establish whether the cause of death was cancer-related or not. Hence, based on these findings, it is difficult to speculate whether epidural analgesia had a clinically meaningful impact on cancer recurrence.

The drawbacks of many of the current studies are that there are many confounding factors, including tumor biology, allogeneic blood transfusions, other concomitant medications, and the role of neoadjuvant and adjuvant anticancer therapies. There could a number of hidden confounders not factored into a multivariate analysis of retrospective, observational, non-randomized data. General anesthetics are multi-modal, and even the use of regional anesthesia is almost always supplementary to general anesthesia. The role of intrathecal and epidural opioids commonly used in regional analgesia and pain management has not been explored. While anesthetics and opioids seem to play a role in promoting tumor growth in isolated cell lines and in animal models, extrapolation to the patient with cancer where multiple networks and interactions exist may be simplistic. It must also be determined whether the pro-tumor effect of anesthetics and opioids observed in the laboratory are likely to make an impact on survival in patients in the real world receiving potent anticancer chemotherapy, molecular-targeted therapies, and hormonal therapies that are prescribed to cancer patients.

On the other hand, it could be argued that if making a relatively minor change to anesthetic practice has the potential to reduce cancer recurrence even to a small extent, it is logical to do so. Taken together, current data are sufficient only to generate a hypothesis that an anesthetic technique during primary cancer surgery could affect recurrence or metastases.[3] Prospective RCTs are needed to answer these questions. There are at least three ongoing RCTs in breast, lung, and colon cancer (NCT 00418457, NCT 01179301, NCT 00684229), and we await their results over the next 1-5 years with great interest.

What Should Clinicians Do?

The role of uncontrolled pain in immunosuppression appears to be greater than that of individual anesthetic agents. Certainly, the role regional anesthesia and analgesia can be expanded where appropriate and used to ensure optimal analgesia and hemodynamic stability. Patients receiving opioids for appropriate clinical indications should continue to receive them, and there should be no denial of pain relief to cancer patients. Volatile anesthetics may be given, and while total intravenous anesthesia with propofol appears attractive where easily applicable and appropriate, it must be kept in mind that concomitant administration of an opioid will also be necessary.

Thus, while the basic science literature does point towards a potential detrimental effect of anesthetic technique on cancer outcomes, current data do not call for a drastic change in the perioperative management of cancer patients.

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