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ANESTHESIA, PAIN MANAGEMENT AND LONG-TERM OUTCOMES (VNR GOTTUMUKKALA AND ER MARIANO, SECTION EDITORS)

Anesthetic Techniques and Long-Term Oncological Outcomes

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Abstract

Purpose of Review Cancer is a leading cause of death, accounting for nearly one in six deaths worldwide. Surgery is a critical intervention in cancer care since it provides a chance of cure or can be used to relieve symptoms in patients with advanced malignancies. Anesthesia (general, regional, or local) and analgesia in any of its delivery modes play critical roles in the treatment and palliation of cancers.

Recent Findings Experimental data demonstrate that surgery itself and anesthetics can promote the growth of micro-metastatic diseases and the seeding of circulating cancer cells, thereby facilitating cancer progression. While this theory originates from in vitro and animal studies, evidence in humans has remained controversial until recently.

Summary In this report, we summarize current published evidence on the impact of anesthetics and opioids on cancer progression. We focus our discussion on published human studies with special emphasis on randomized controlled trials.

Keywords Cancer · Recurrence · Surgery · Anesthesia · Opioids

Introduction

Cancer is one of the leading causes of mortality worldwide, with more than 90% of all deaths associated with metastatic or recurrent disease [1]. Despite all the advances in cancer treatments such as chemotherapy, radiation therapy, and immunotherapy, surgery remains the mainstay for non-metastatic disease as it offers the best chance for long-term survival of patients with solid tumors. However, it has been suggested that surgical interventions could have an unexpected deleterious impact on cancer recurrence, either by increasing micrometastasis and metastatic foci from shredding of tumor into circulatory systems during surgical manipulation of tumor or through activation of the hypothalamic–pituitary–adrenal (HPA) axis with release of inflammatory mediators and immunosuppressive factors associated with tissue damage [2].

Major cancer surgical procedures require the administration of inhalational, intravenous, or local anesthetics to provide unconsciousness and anti-nociception during surgery. There has been a great deal of interest in determining if the choice of anesthetic technique could reduce the potential negative aspects of surgical stress and tissue damage [3]. In addition to their desired effects, anesthetic agents also have direct and indirect effects on the immune response by inhibiting the activity of natural killer (NK) cells or by activation of the HPA axis [4, 5]. Anesthetics also modify cellular processes involved in metastasis; through this mechanism, it has been suggested that anesthetics could interfere with cancer outcomes such as recurrence-free survival (RFS) or overall survival (OS) [3].

The purpose of this article is to review the current evidence investigating the various anesthetic techniques and their impact on long-term oncological outcomes. We will focus on specific categories of anesthetic agents: propofol-based total intravenous anesthesia (TIVA), volatile agents, intravenous anesthetic adjuvants (lidocaine, dexmedetomidine, and ketamine), regional anesthesia, and opioids. We will summarize pertinent findings from retrospective studies

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and meta-analyses and focus our discussion on the available randomized controlled trials (Table 1).

TIVA Versus Volatile Agents

Propofol and volatile anesthetics are the most frequently used anesthetic agents worldwide to provide general anesthesia for surgical and procedural care. The role of these hypnotic drugs in cancer recurrence has received considerable focus in recent years with numerous preclinical investigations, several retrospective studies, and one randomized controlled trial to date [6]. The data from preclinical studies suggest that inhalational anesthetics enhance proliferation, migration, and angiogenesis of cancer cells while suppressing immune cell function [4, 7]. In contrast, propofol-based anesthesia has been shown to antagonize cancer proliferative pathways while preserving immune function [4, 8].

Data from retrospective studies are mixed and controversial. Most of these studies were statistically underpowered and suffered from significant confounding. To address some of the limitations of these individual retrospective studies, meta-analyses have been conducted but have shown conflicting results [6, 9]. For instance, Yap et al. pooled data ($N=7866$) from nine retrospective studies and one small RCT including patients who underwent breast, esophageal, gastric, colon, rectal, and non-small cell lung surgery to investigate OS and RFS for volatile anesthetics versus TIVA [6, 9]. Despite the attempt to comprehensively cover this topic, the inherent problem with any meta-analysis is the quality and heterogeneity of the component studies that were included in the study. Therefore, it is difficult to extrapolate or draw definitive conclusions as to the impact of propofol-based TIVA compared to volatile anesthetics on cancer outcomes.

Among the retrospective studies, Wigmore et al. investigated the long-term effect of propofol-based TIVA versus volatile anesthetics for cancer surgery [10••]. The study was conducted in a comprehensive cancer center. Patients who received both forms of anesthesia were excluded from the study [10••]. Propensity score matching was performed ($N=2607$ per group), and univariate and multivariable regression models were used to compare hazard ratios (HR) for death. After multivariable analysis, patients in the volatile anesthetic group compared to the propofol-based TIVA group had a HR of death of 1.46 (95%CI: 1.29–1.66). This association between the use of volatile anesthesia and survival remained in a subgroup analysis that included patients with and without metastatic disease [10••].

More recently, Makito et al. conducted the largest retrospective study to date assessing the impact of volatile anesthesia versus propofol-based TIVA in cancer patients undergoing digestive cancer surgery [11]. Patients were selected from the Japanese Diagnosis Procedure Combination database from 2010 to 2018. All patients in this study had undergone elective digestive cancer surgery: esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, and rectal cancer surgery [11]. A total of 196,303 patients were eligible for the study, with 166,966 patients in the volatile anesthetic group and 29,337 in the propofol-based TIVA group [11]. The overall rates of death in volatile anesthetic and propofol-based TIVA groups were 10.4% and 11.4%, respectively. TIVA was not associated with improved RFS in Cox regression analysis, but there was statistically significant improvement when instrumental variable analysis was applied, albeit without clear clinical benefit [11].

In contrast to previously published retrospective studies, a large multi-center randomized controlled trial conducted in 14 centers in China investigated the effects of volatile

Table 1 Summary of randomized controlled trials investigating the effect of regional/local anesthesia on cancer recurrence

Author/year	Cancer	Intervention	Sample size	Finding
Sessler, 2019	Breast	Regional anesthesia (paravertebral blocks/epidural) plus general anesthesia vs. volatile anesthesia	2108 women	No difference in cancer recurrence
Yu. 2023	Breast	PEC block vs. no PEC	526 women	No difference in cancer progression
Badwe, 2023	Breast	Peritumoral lidocaine infiltration vs. no infiltration	1583 women	Peritumoral infiltration with lidocaine prolonged DFS
Xu, 2021	Lung cancer	General anesthesia plus epidural vs. general anesthesia alone	400 patients	No differences were found for RFS and OS
Falk, 2021	Colorectal cancer	Thoracic epidural analgesia vs. intravenous morphine analgesia	221 patients	No differences were found for DFS
Du, 2021	Thoracic and abdominal cancers	General anesthesia plus epidural vs. general anesthesia alone	1712 patients, mostly colorectal cancers	No differences were found for RFS

PEC pectoral nerve block, *DFS* disease-free survival, *RFS* recurrence free survival, *OS* overall survival

anesthesia and propofol-based TIVA in 1195 patients [12]. Patients 65 to 90 years old who were thought to have primary solid-organ non-neurologic cancer, who had not previously been treated with either radiation or chemotherapy, and were scheduled to have primary cancer surgery with general anesthesia expected to last at least 2 h were included in this study. The primary endpoint of the trial was OS, and secondary endpoints included RFS. Patients were followed for 3 years after surgery. The authors concluded that survival after major cancer surgery was similar for both volatile anesthesia and propofol-based TIVA groups (adjusted HR: 1.02, [95% CI: 0.83–0.834]) [12].

In summary, the presumed benefits of propofol-TIVA alone on cancer recurrence or progression may not be clinically significant.

Intravenous Anesthetic Adjuvants

Intravenous anesthetic adjuvants, such as lidocaine and dexmedetomidine, are commonly administered to patients with cancer requiring surgery to provide analgesia and reduce consumption of primary anesthetic agents. Intravenous lidocaine has gained significant notoriety because of its well-known opioid-sparing effects [13]. Additionally, lidocaine has been shown to have modest anti-inflammatory effects, improve the cytolytic activity of NK cells, reduce neutrophil extracellular traps, and exert cytotoxicity against cancer cells [14–17]. As a consequence of the potential anti-cancer effects of lidocaine, various studies have been conducted to determine if the intravenous infusion of lidocaine could improve oncological outcomes in patients with cancer requiring surgery with curative intent [18–20]. In a randomized controlled trial, Zhang et al. randomized patients ($N = 563$) with pancreatic cancer to receive intravenous lidocaine (1.5 mg/kg bolus at induction of general anesthesia, followed by a continuous infusion of 2 mg/kg/h or placebo intraoperatively [19]. Lidocaine did not show beneficial effects in DFS (HR: 0.91, [95% CI: 0.71–1.17) and OS (HR: 0.98, [95% CI: 0.81–1.17) [19]. A limitation of this study was that lidocaine was only administered intraoperatively and not continued after surgery. It remains unknown whether extending the duration of infusion of lidocaine confers any beneficial effects on cancer progression.

The effect of dexmedetomidine in cancer progression is also an area of extensive research. Experimental evidence suggested that dexmedetomidine could affect—either by promoting or suppressing—mechanisms related to metastasis [21, 22]. A retrospective study in patients with non-small cell lung cancer showed worsened OS with no significant impact on RFS [23]. A follow-up small randomized controlled trial ($N = 55$) showed no significant effect of dexmedetomidine (loading dose of 1 mg/kg followed by a continuous infusion of 0.3 mg/kg/h) compared to placebo in colorectal cancer progression [24]. Li et al. investigated the effect of intraoperative dexmedetomidine on long-term survival in older patients after major noncardiac surgery in a 3-year follow-up of a randomized controlled trial. In the study, 619 patients with a variety of cancers were followed up for 42 months, and oncological outcomes and mortality were evaluated retrospectively. The study showed that dexmedetomidine administration was associated with improved RFS (adjusted HR: 0.56, 95%CI: 0.39–0.79) but not OS (adjusted HR: 0.77, 95%CI: 0.5–1.17) [25].

Ketamine is also used as an anesthetic adjuvant because of its opioid- and general anesthetic-sparing effect [26]. In a retrospective study of patients undergoing surgery for adenocarcinoma of the lung, intraoperative ketamine use was associated with improvement in RFS (HR: 0.44, 95% CI: 0.24–0.80) [26]. In women with breast cancer, the administration of ketamine did not influence cancer progression [27]. Cho et al. investigated the impact of ketamine on long-term biochemical (carcinoembryonic antigen) recurrence in patients having colorectal cancer surgery [28]. One hundred patients were randomly assigned to either the ketamine (0.25 mg/kg bolus followed by a continuous infusion at 0.05 mg/kg/h) or placebo. The study showed no difference in 6-, 12- and 24-month measured circulating concentrations of the carcinoembryonic antigen [28].

Altogether, emerging data suggest that the administration of lidocaine during surgery purely to improve oncological outcomes is not justified. Whether dexmedetomidine or ketamine can provide oncological benefits in patients with cancer requiring surgery remains unknown.

Regional Anesthesia

Surgery has been associated with the release of inflammatory mediators and other factors that help to promote the spread of cancer [3]. Regional anesthesia reduces or eliminates the requirement for general anesthetic agents and opioids and can modulate the neuro-endocrine stress response associated with surgery [29••, 30–32]. In addition, the administration of local anesthetics has also been associated with inhibiting tumor growth, proliferation, and metastasis in animal models [14, 33]. Local anesthetics also are associated with preserving immune function as evidenced by in vitro studies [14, 33]. Therefore, it has been postulated that performing oncological surgeries using regional anesthesia could decrease cancer recurrence rates when compared to general anesthesia alone [34].

Several retrospective studies have investigated the potential survival benefit of using regional anesthesia for cancer removal surgery with mixed results [35–37]. A

sub-study of a randomized controlled trial by Christopherson et al. evaluated if epidural analgesia was associated with decreased cancer recurrence following colon cancer resection [38]. The authors found a beneficial association between epidural analgesia and improved survival in patients without metastases. However, the study did not show any improvement in survival for patients with metastases [38]. Myles et al. also conducted a sub-study of a multi-center randomized controlled trial (MASTER trial) to investigate if the use of epidural anesthesia for surgical removal of abdominal cancer would improve cancer-free survival as well as overall survival. The study showed no difference in 5-year cancer recurrence and mortality rates [39].

In 2019, the results of a randomized controlled trial conducted by Sessler et al. evaluating the use of regional anesthesia in breast cancer surgery patients were published. In that study, 2108 women undergoing primary breast cancer resection ($N = 2132$) were randomized into a regional anesthesia-analgesia group (mostly paravertebral blocks) or a general anesthesia-opioid analgesia group (mostly sevoflurane volatile anesthesia) with the aim to assess local and metastatic cancer rates between the two groups. No difference was noted in breast cancer recurrence (HR: 0.97 [95% CI: 0.74–1.28]) between the groups [29••]. Yu et al. conducted a randomized controlled trial in 526 women with breast cancer surgery to determine if the combination of interpectoral plane and pectoserratus plane blocks, also known as the "Pecs II" block, would have any effect on cancer outcomes; this fascial plane block combination had no effect on RFS (HR: 0.9 [95% CI: 0.76–1.32]) [40]. Karmakar et al. also reported no difference between the thoracic paravertebral block and general anesthesia groups for women ($N = 180$) undergoing modified radical mastectomy with 5-year follow-up [41].

More recently, a randomized controlled trial ($n = 400$) in patients undergoing video-assisted thoracoscopic lung cancer resection investigated the effect of general anesthesia plus epidural versus general anesthesia alone on RFS and OS. No differences were found for RFS (HR: 0.90, 95% CI, 0.60–1.35) or OS (adjusted HR: 1.12; 95% CI, 0.64–1.96) [30]. Another important study randomized patients ($N = 1712$) with thoracic and abdominal cancers (mostly colorectal) to general anesthesia alone or general anesthesia plus thoracic epidural analgesia [42]. Again, regional anesthesia did not improve recurrence-free survival (HR: 0.97 [95% CI: 0.84–1.12]). In a multi-center study, patients ($N = 221$) scheduled for elective colorectal cancer surgery were randomized to thoracic epidural analgesia versus intravenous morphine analgesia [43]. The primary endpoint was disease-free survival at 5 years after surgery. The study showed no differences survival (adjusted HR: 1.19, [95% CI: 0.61–2.31) [43].

Lidocaine infiltration has demonstrated anti-tumor effects in vitro and in vivo [14–17]. Badwe et al. randomized 1583 women with early breast cancer who underwent tumor resection to receive a peritumoral injection of 0.5% lidocaine 7–10 min prior surgery or a control group who did not receive an injection of the local anesthetic. Peritumoral injection of lidocaine increased disease-free survival (HR: 0.74; [95% CI 0.58–0.95]) and OS (HR, 0.71 [95% CI, 0.53–0.94]) [44]. While the results from this study are certainly important, the lack of a true placebo group (e.g., saline injection) is a major limitation.

To summarize what is currently known in terms of regional anesthesia and cancer outcomes, data from five randomized controlled trials demonstrate that regional anesthesia may not directly improve oncological outcomes although there may be other indirect benefits. However, it remains an open hypothesis whether or not peritumoral administration of local anesthetics can influence cancer progression.

Opioids

The mu-opioid receptor (MOR) is one of the most studied proteins in medicine. MORs, which are well-known for their role in mediating the analgesic effects of opioids, are found not only in neurons but also in immune and cancer cells. Preclinical studies indicate that the regulation of MOR expression in cancer cells may be associated with tumorigenesis and metastasis [45, 46]. Clinical studies, though often limited in design, suggest that high levels of MOR expression could be an independent risk factor for poor survival in patients with certain cancers, including prostate, larynx, and lung cancer [47–49]. A retrospective analysis by Zylla et al. also suggested that the MOR expression level was independently associated with PFS and OS in prostate cancer patients. Authors reported that each 1% increase in MOR expression increased the risk of tumor progression or death by 65% and 55%, respectively [48]. However, this was not evident in patients with pancreatic adenocarcinoma or colorectal cancers [50, 51].

Currently, the American Society of Clinical Oncology (ASCO) recognizes that "opioid therapy is generally the first-line approach for moderate to severe chronic pain associated with active cancer" [52]. ASCO also recommends that opioids can be prescribed in select cancer survivors with post-cancer or post-treatment pain syndromes [53]. The relationship between opioid use and cancer progression is a subject of investigation. Some studies suggest a negative association between opioid use and cancer progression in specific cancer types, while others indicate a worse prognosis in patients with high perioperative or persistent postoperative opioid use. The impact of opioids on cancer outcomes appears to vary between different

types of cancer. High opioid use is associated with poor survival in pancreatic cancer but not necessarily in breast, oral, or colorectal cancers.

A negative association between opioids and cancer progression has been demonstrated for patients ($N = 362$) with laryngeal squamous cell carcinomas [54]. In patients with non-small lung cancer, two ($N = 901$ and $N = 2884$) retrospective studies demonstrated that high perioperative opioid use and persistent postoperative use of prescription opioids are associated with a worse prognosis [55, 56]. Connoly et al. showed that high intraoperative use of opioids was significantly associated with worse overall survival (HR: 1.09/10 morphine milligram equivalents, 95% CI: 1.02–1.17) [26]. In that study, aberrant intracellular signaling was associated with better RFS at higher opioid use [26]. In patients with advanced pancreatic cancer, high opioid use was also associated with poor survival [57].

In contrast, other studies have shown no association between the use of opioids and worse outcomes for breast and oral cancers [57, 58]. Intraoperative opioid consumption did not influence DFS (HR = 0.852, 95% CI 0.655–1.11) in colorectal liver metastasis patients ($N = 110$) treated with simultaneous resection of their primary tumor [59]. A retrospective investigation of children and adolescents undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy showed similar results [59]. A large sample retrospective study pointed out that among 725 patients undergoing esophageal cancer surgery, a high dose of opioids during surgery (≥ 710 μg) was associated with longer survival. In a meta-analysis of retrospective studies comparing patients with no opioids versus high- or low-dose opioid use, high-dose opioid use was associated with a worse PFS (HR = 1.086, 95%CI 1.011–1.166) and OS (HR = 1.006, 95%CI 1.001–1.012) [60]. Rangel et al. conducted the first randomized controlled trial to determine if avoiding opioids (opioid-free anesthesia) intraoperatively versus opioid-based anesthesia in patients ($N = 143$) with localized prostate cancer with moderate or high risk of biochemical recurrence would improve biochemical free survival. The key finding from the study is that opioid-free anesthesia did not influence biochemical recurrence-free time (HR: − 1.03, 95% CI: 2.65–0.49).

Some studies involving MOR antagonists, such as methylnaltrexone, show potential benefits in improving overall survival, while others, like a small phase II study with naltrexone in advanced breast cancer, did not demonstrate significant oncological benefits [61].

Despite conflicting findings, opioids continue to be used in patients with moderate-to-severe cancer-related pain due to the uncertainty surrounding their potential negative impact on oncological outcomes.

Conclusion

Laboratory work and animal studies have provided us a better understanding of the role of neuro-humoral signaling and perioperative inflammatory-immune responses on cell and cancer biology. Anesthetic agents, local anesthetic drugs, opioid agonist medications, ketamine, and dexmedetomidine have pharmacological actions that can affect the inflammatory and immune system, which may be relevant to cancer outcomes through cellular and sub-cellular pathways and mechanisms. Regional anesthesia and analgesia techniques have been hypothesized to affect the perioperative inflammatory-immune responses in a positive way and improve oncological outcomes by obtunding the neuro-humoral and metabolic stress responses to surgery.

While different anesthetic techniques and analgesia regimens may offer clinical benefits by sparing opioids, minimizing symptom burden, and reducing overall morbidity and mortality in select patient populations, to date, there is no convincing evidence that any one anesthetic strategy or technique influences cancer outcomes in a positive manner. However, this is an exciting time for anesthesiology and perioperative medicine as there is growing interest in research on anesthetic strategies and long-term clinical outcomes, and there is opportunity to expand the role of perioperative medicine in improving population health.

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Declarations

Competing interests The authors declare no competing interests.

Ethics Approval and Consent to Participate Not applicable

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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