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The role of regional anesthesia in the propagation of cancer: A comprehensive review

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New cancer incidences worldwide will eclipse 18 million in 2019, with nearly 10 million cancer-related deaths. It is estimated that in the United States, almost 40% of individuals will be diagnosed with cancer in their lifetime. Surgical resection of primary tumors remains a cornerstone of cancer treatment; however, the surgical process can trigger an immune-suppressing sympathetic response, which promotes tumor growth of any residual cancerous cells post surgery. Regional and local anesthesia have become staples of anesthesia and analgesia during and after surgery. Recently, much evidence in the form of retrospective and prospective studies has come to light regarding the protective, antitumor properties of anesthetic and analgesic agents across a wide variety of cancers and patient demographics. It is believed that by blocking afferent pain signals, the body does not mount the sympathetic response that contributes to the perpetuation of disease after surgical treatment. This review, therefore, investigates these studies as they pertain to the treatment and outcomes of cancers treated surgically to elucidate the role of regional anesthesia in the propagation of cancer.

Introduction

New cancer incidences worldwide will eclipse 18 million by 2019, with approximately 10 million cancer-related deaths [1]. It is estimated that in the United States, approximately 40% of individuals will be diagnosed with cancer in their lifetime [1]. Many people with cancer who end up in remission face the sobering reality of possible recurrence, which varies widely between cancer types. Glioblastoma recurs in almost 100% of patients, despite treatment. In this regard, malignant melanoma and ovarian cancer both have more than 80% recurrence rates. Breast cancer has a 30% recurrence rate and colorectal cancer has a 17% recurrence rate after curative surgical resection with microscopically clear margins. Cancer recurrence is a serious problem involving multiple mechanisms and much effort has been made to ascertain what role anesthesiologists play in preventing recurrence rates [1].

Surgical resection of primary tumors remains a cornerstone of cancer treatment [2]. Surgery is a known vector of cancer recurrence and growth, which occur by two mechanisms. Direct dissemination of micrometastasis can occur after surgery. Furthermore, surgery activates the sympathetic nervous system and hypothalamic-pituitary axis, thereby suppressing immune function and promoting growth of remaining minimal residual disease [3,4]. Minimal residual disease is occult, *in situ* tumor that remains after primary tumor surgical excision and spreads via hematogenous or microstromal mechanisms [3].

Regional anesthesia and analgesia are cancer protective

The perioperative period consists of three phases: a preoperative period, intraoperative period, and postoperative period. A tremendous effort has been made, especially during the enhanced recovery after surgery era, to hasten early recovery by attempting to maintain preoperative organ function and decrease the stress response to surgery. This is achieved by a multimodal, multistep process that includes preoperative oral pain medication and carbohydrate loading, a regional anesthetic or neuraxial block potentially designed to reduce postoperative pain and opioid consumption, and reduced hospital stays. General endotracheal anesthesia with volatile gases and intravenous pain medications (e.g., opioids, ketamine, and dexmedetomidine) are usually used intraoperatively. Finally, a multimodal pain regimen is employed in the postoperative period.

Regional anesthesia consists of local anesthetics (e.g., lidocaine, bupivacaine, and ropivacaine) that block peripheral or spinal nerve transmission, which, in turn, blunts the sympathetic response to surgery and subsequent hypothalamic-pituitary axis activation. This augmentation in afferent pain signaling, avoidance of immune suppression, and reduction of inflammatory markers, as well possible direct effects of local anesthetics on cancer cells, influence the recurrence of cancer that is currently unclear. The clinical importance and complete picture of the effect of regional anesthesia on cancer recurrence is not currently known due to the paucity of randomized controlled trials (RCTs). There are several RCTs that have finished enrolling study participants; however, some RCTs are still collecting data and others are within the follow-up period [5–11]. Most of these studies are estimated to be completed by 2023 [5–11].

The human immune system can identify and eliminate nascent tumors. Yet, the mechanisms involved in achieving these processes have been highly debated [12]. Immunoediting, a process where T-cell recognition of tumor antigens influences the immunogenicity of tumor cells, has emerged as the accepted fundamental concept of the immune system's antitumor response. There are 3 stages in immunoediting, namely *elimination*, *equilibrium*, *and escape* [13]. The *elimination* phase, classically known as immunosurveillance, involves innate and adaptive immune responses such as natural killer (NK) cells and T cells. Tumor cells and macrophages secrete inflammatory cytokines, such as interleukin-12 (IL-12) and interferon gamma (IFN-γ), which activate NK and T cells resulting in tumor cell death by cytotoxic mechanisms [14]. In the *equilibrium* stage, which can last for years, non-immunogenic cancer cells that have acquired resistance to elimination are held in check by the immune system but they cannot be eliminated and remain in a dormant state [14]. These resistant cells, in the future, can enter the *escape* stage where tumor cells evade the immune system, possibly experience uncontrolled growth, and evolve into malignancies [14]. The perioperative period poses a threat to each stage of immunoediting by causing T-cell, B-cell, and NK-cell dysfunction for several days following surgery [14–17]. Surgery decreases the amount of NK cells and T cells due to increased caspase-3 activity, resulting in programmed cell death [18]. Painful stimuli during surgery also reduce the cytotoxic activity of NK and T cells [19–21]. Volatile anesthetics have been shown to depress NK-cell function, induce T-cell apoptosis, and increase the gene expression of proinflammatory cytokines [22–27]. Volatile anesthetics are known to suppress immune function and cell-mediated immunity [28–31]. Opioids such as morphine suppress NK-cell cytotoxicity, promote macrophage and T-cell apoptosis, and stimulate tumor cell migration and proliferation *in vitro* [32].

Tumorigenesis occurs when multiple cellular abnormalities accumulate over time until a cell mass can function independent of the surrounding tissue. Initially, cells maintain sustained proliferative signals. This can occur in various ways, including proto-oncogenes undergoing a gain-of-function mutation, cells losing dependence on exogenous growth factors—termed autocrine signaling, or overexpression of cell surface tyrosine kinases leading to growth factor hypersensitivity [33]. Mutations of membrane-bound tyrosine kinases (e.g., human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGF-R)) can also allow intracellular signaling without proper ligand binding on the cell membrane [34]. Similarly, tumor cells will evade growth-suppressing signals. Important cell cycle regulators such as retinoblastoma (Rb) protein frequently have loss-of-function mutations in cancer. Without regulation in the cell cycle, cells proliferate completely unchecked leading to potential tumor development [33,34]. Further cell cycle dysfunction can occur with mutation in Rb protein regulators, in particular TGF-β and its receptor. In the healthy cell, DNA repair mechanisms recognize these mutations and seek to reverse them before DNA can be further replicated. During tumorigenesis, however, defective DNA repair mechanisms further contribute to genomic mutation and instability. The tumor suppressor gene, TP53, is crucial for the proper function and maintenance of this machinery, and it represents the most commonly mutated gene across all human cancers [34,35]. Another role of TP53 is the induction of apoptosis, a programmed cell death mediated by caspases to avoid further propagation of the mutated cell [33,35]. Apoptosis can be triggered by DNA damage, insufficient production of survival factors, hypoxia, or intracellular signal imbalance from oncogene activation [33]. When these conditions are recognized by the cell, death signals, including FAS-ligand/FAS-receptor binding and TNFα/TNF-receptor binding, cause caspase release, thereby inducing apoptosis. Mutations and overexpression of survival factors (e.g., Bcl-2) are oncogenic, and they prevent caspase activation, thereby halting apoptosis [33].

Tumor growth, metastasis, and proliferation depend on angiogenesis and lymphangiogensis, which involve neovascularization and new lymphatic vessel growth to provide nutrients for cell growth. Angiogenesis is triggered by chemical signals originating from tumor cells [32]. Vascular endothelial growth factor A (VEGF-A), also known as VEGF, is the major mediator in tumor angiogenesis and is present in most types of human cancer. Increased expression of VEGF by tumors is associated with a less favorable prognosis [36]. Induction or enhanced proliferation of VEGF receptors can occur by a variety of factors such as hypoxia, inflammatory cytokines (i.e. IL-6), chemokines, and growth factors [37]. Hypoxia is a common characteristic of solid tumors that stimulate VEGF production via hypoxia-inducible transcription factors 1α and 2α [37].

Tumor cells must also become immortal because normal human somatic cells have a finite replicative capacity [34]. This is mainly due to a loss of genetic material at the end of chromosomes during each replication because of the inability of replication machinery to completely copy each chromosome. After many rounds of replication, the genetic material that is lost triggers the cell to die by apoptosis [34]. In 85%–90% of human cancers, immortality is achieved through activation of telomerase [34]. The enzyme adds base pairs to the end of the chromosomes after replication has occurred, thereby protecting them from natural degradation during the replication process [34]. Alterative recombination is another method by which tumors can maintain telomere length to achieve immortality [33,34].

Other important tumorigenic processes include pro-tumor inflammation and dysregulation of cellular metabolism [34]. The Warburg Effect describes a tumor's metabolic reliance upon glycolysis even in aerobic conditions [38]. Even though this is inefficient in producing ATP compared with the citric acid cycle in mitochondria, it does provide the tumor with the advantage of creating massive amounts of metabolic intermediates that can be used to synthesize important molecules, such as amino acids and nucleic acids, and maintain the rapid proliferative rates observed in tumor cells [34,38]. The switch in metabolism often occurs due to RAS mutation or hypoxic conditions, both of which are common in human cancers [34]. These increase the amount of HIF-1α and HIF-2α in the cell, which act as transcription factors. Among their targets are the glycolytic enzymes and GLUT1 [34]. Inflammation is common at the site of tumors, and it supplies the tumor with important bioactive molecules, including survival factors, growth factors, angiogenic factors, and extra-cellular matrix (ECM) modifiers [34]. These are all important for tumor progression and metastasis. Inflammation also causes the release of reactive oxygen species (ROS) and other mutagens that can accelerate the rate of mutation within the tumor and surrounding tissue, leading to faster tumor progression [34].

Lidocaine and other local anesthetics are known to have analgesic and antiinflammatory properties when used in the perioperative period. The local anesthetic's primary action is to inhibit sodium influx through sodium-specific ion channels. Lidocaine has demonstrated direct effects on cancer growth rate and invasiveness. High expression of voltage-gated sodium channels (VGSCs) is noted in aggressive carcinomas of prostate cancer, breast cancer, lymphoma, small cell and non–small cell lung cancer, mesothelioma, neuroblastoma, melanoma, and cervical cancer [39]. One mechanism potentially explaining this phenomenon is stimulation of VGSCs on malignant cells eliciting changes in intracellular pH and calcium homeostasis, which then improves motility, metastasis, and invasion [40]. Lidocaine also suppresses tyrosine kinase activity of epidermal growth factor receptor (EGFR). Low EGFR activity results in a reduction of cell proliferation, and higher lidocaine doses are proved cytotoxic to cancer cells [41].

Studies in specific cancer surgery

Tumor manipulation during colorectal surgery has been shown to be associated with the release and dissemination of tumor cells through the vascular and lymphatic systems [2]. Studies have also shown a clear correlation between the number of circulating tumor cells and gastrointestinal cancer [3]. Detection of tumor cells in circulation was also associated with a worsened prognosis in colorectal cancer patients undergoing chemotherapy [4]. The perioperative period, thus, provides a beneficial milieu for colorectal tumor spread and recurrence in the future.

Colorectal cancer

Prospective studies

There is a lack of good-quality, prospective RCTs examining the effectiveness of epidural analgesia in improving colon cancer survival and reducing cancer recurrence. Most studies were performed as a revaluation of an original randomized prospective study evaluating the outcomes of the use of epidural analgesia in major abdominal surgeries.

The "MASTER" trial was a multicenter, prospective RCT of epidural anesthesia and analgesia and general anesthesia and postoperative systemic opioids in high-risk patients undergoing major surgery [42]. Epidural analgesia was continued for 3 days after operation. Nine hundred and fifteen patients were originally enrolled in the study between July 1995 and May 2001. Myles et al. [28], in a subset analysis of cancer patients (n = 446, 112 underwent surgery because of stage I–III colon cancer) enrolled in the original MASTER trial and found no association between the use of epidural analgesia and improvement in cancer survival rate [28].

The cooperative study number 345 (CST 345) was a multicenter, prospective, randomized control study to determine whether epidural anesthesia and postoperative epidural analgesia decreased the incidence of death in four types of intraabdominal surgical procedure (aortic, gastric, biliary, and colon surgeries). The investigators found no difference in 30-day survival rates between the epidural group and control group. In sub-analysis of the prospective randomized CST 345 study, Christopherson et al. evaluated the long-term survival of patients with colon cancer and concluded there was an early survival benefit (within 1.46 years) in patients without metastases who received a supplemented epidural analgesia and those patients who were in the general anesthesia only group. Long-term survival benefit was not evident. A total of 177 patients were evaluated in the subanalysis. No short-term or long-term survival benefit was found in those patients with colonic cancer with distant metastases.

Similarly, Binczak et al. performed a subset analysis of patients from an original single center, prospective, randomized study designed to evaluate the benefit of epidural analgesia versus systemic opioids on postoperative pain and adverse events after major abdominal surgeries [29,30]. One hundred and thirty-two patients were included in the subset analysis, of which 55 patients underwent surgery for colorectal cancer. Investigators failed to demonstrate the benefit of epidural analgesia combined with general anesthesia on recurrence- or metastasis-free survival after abdominal cancer surgery.

Retrospective studies

In a retrospective study, Tai et al. evaluated the association effect of epidural analgesia on recurrence of cancer and overall survival in stage IV colorectal cancer [31]. A total of 999 patients were included in the study, of which 165 patients received epidural analgesia. Median follow-up time was 17.5 months. Investigators found no significant differences in postoperative progression-free survival and overall survival. A significant number of patients in this study did not receive epidural analgesia due to either contraindications or technical difficulties. In another retrospective analysis of 510 patients (390 of which received epidural analgesia) undergoing hepatic resection for metastasis, Zimmitti et al. found an improved 5-year recurrence-free survival rate of 34.7% in the epidural group and 21.1% in the intravenous analgesia only group [5]. There was no significant difference in the overall survival. Due to the retrospective nature of these studies, patients were not randomized and clinical care was not standardized.

Primary hepatocellular cancer

There are very few studies evaluating the use of regional anesthesiology in hepatocellular cancer. The propensity for coagulopathy may serve as a deterrent for the use of neuraxial and paravertebral blockade in this patient group.

Chang et al. in a retrospective study evaluated 744 medical records at a single medical center. Median follow-up time was 64.5 months [6]. Investigators did not find a significant association between the use of epidural analgesia and recurrence-free survival or overall survival. Similarly, Lai et al., in a retrospective study of patients undergoing radiofrequency ablation for hepatocellular cancer, found no change in recurrence-free survival or overall survival between the general anesthesia and epidural anesthesia groups [7].

Gastric and esophageal cancer

In a retrospective study, Wand et al. evaluated the records of 273 patients who had undergone gastric cancer surgery [8]. The general anesthesia group comprised 116 patients and the epidural-supplemented group comprised 157 patients. Patients were followed up to death; the longest follow-up period was 8 years. Investigators found no difference in long-term survival rates between the two groups. Cummings et al., in a population-based study using Current Procedural Terminology codes to identify epidural placement, identified 2745 patients, of which 766 had epidural codes. Investigators found no difference in recurrence or survival among the two groups [9].

In another retrospective analysis in patients who had surgery for esophageal cancer, after evaluating 153 patients (118 received epidural analgesia) Heinrich et al. found no association between the use of epidural analgesia and cancer recurrence or 5-year survival [10]. In contrast, Hiller et al. reported a significant improvement in the rate of tumor recurrence in those patients who received an epidural analgesia for gastroesophageal cancer surgery. In their retrospective study, an effective epidural following esophagectomy was associated with reduced risk of cancer recurrence within 2 years (HR 0.34; 95% CI: 0.16–0.75, $P = 0.005$). This effect was not seen in patients with gastric cancer (HR 1.19; 95% CI: 0.42–3.33, $P = 0.75$).

Prostate cancer

In a secondary analysis of subjects undergoing radical prostatectomy, who had participated previously in a randomized controlled trial, Tsui et al. [43] evaluated 99 charts of patients comparing epidural with general anesthesia and general anesthesia alone for radical retropubic prostatectomy [11]. Investigators concluded that the secondary analysis showed no advantage in preventing biochemical recurrence of prostate cancer resulting from the adjunctive use of epidural analgesia at the time of radical prostatectomy. Either the study was underpowered or there is no real beneficial effect of epidural analgesia during prostate surgery for cancer.

Retrospective studies—spinal

Tseng et al. performed a retrospective review of 1166 and 798 patients with prostate cancer who underwent radical prostatectomy using either a spinal anesthesia with sedation ($n = 1166$) or general anesthesia ($n = 798$) [44]. They found no difference in prostate cancer recurrence between the groups. Patients who received general anesthesia tended to have more advanced disease, as evidenced by significantly more advanced clinical stage, higher biopsy, and pathologic Gleason sum. One of the strengths of the study is the large sample size, and limitations include the retrospective nonrandomized nature of the study and the inability to capture and account for other factors (e.g., temperature and blood administration) that may contribute to perioperative cancer recurrence. In another large retrospective study, Roiss et al. evaluated 4772 prostate cancer surgery patients who were stratified into two groups: 1725 patients underwent general anesthesia alone and 3047 underwent spinal anesthesia combined with general anesthesia [45]. They reported no statistically significant difference between the two groups for biochemical recurrence-free survival, metastasis-free survival, and overall survival. Total intravenous anesthesia (TIVA) was administered more frequently within the spinal group. Higher blood transfusion rates were documented within the general group. In addition, higher blood loss and higher transfusion rates were recorded within the general patients.

Retrospective studies—epidural

Sprung et al. reviewed a group of 486 patients who underwent radical retropubic prostatectomy performed under epidural anesthesia [46]. They were matched equally based on age, surgical year, and baseline prostate cancer pathology to patients who had general anesthesia. Compared with general anesthesia with systemic opioids, epidural anesthesia and analgesia with fentanyl was not associated with improvement in long-term oncologic outcomes. In contrast, Biki et al., in a retrospective review of medical records of patients who had a radical prostatectomy, concluded that the epidural plus general anesthesia group had a lower rate of biochemical recurrence as measured by prostate-specific antigen levels when compared to the general group without epidural analgesia [13]. Follow-up interval ranged from 2.8 to 12.8 years. After adjusting for tumor size, Gleason score, preoperative PSA, margin, and date of surgery, the epidural plus general anesthesia group had an estimated 57% (95% CI, 17%–78%) lower risk of recurrence compared with the general anesthesia plus opioid group, with a corresponding hazard ratio of 0.43 (95% CI, 0.22–0.83; $P = 0.012$) in the multivariable Cox regression model. Additionally, Scavonetto et al. reported a possible beneficial effect of regional anesthesia in patients undergoing radical prostatectomy [14]. However, in this study, investigators evaluated general anesthesia with neuraxial analgesia (intrathecal and epidural administration) with general anesthesia only. Patients were followed up for a maximum period of 8.6 years. A total of 1642 matched patients were included in the final analysis. When adjusted for covariates, which included individual comorbidities, positive surgical margins, and adjuvant treatment, systemic progression was greater in general anesthesia-only patients (adjusted HR = 2.81, 95% CI 1.31–6.05; $P = 0.008$), as was overall mortality (adjusted HR = 1.32, 95% CI 1.00–1.74; $P = 0.047$).

Bladder cancer

Retrospective, epidural

Chipollini et al. performed a retrospective analysis of 430 patients with clinically nonmetastatic urothelial carcinoma of the bladder who underwent radical cystectomy [15]. Two anesthetic techniques were used, namely perioperative epidural analgesia with general anesthesia versus general anesthesia alone. Epidural patients received a sufentanil-based regimen. Patients with epidural received higher median total intravenous morphine equivalents (75ivMEQ) than those in the general group (50ivMEQ). Epidural anesthesia using sufentanil was associated with worse recurrence and disease-free survival in bladder cancer patients treated with surgery. The authors believe that the immunosuppressive effect of increased systemic opioids because of the use of epidural sufentanil and increased total morphine equivalents led to the poor recurrence and survival outcomes. A majority of recurrences occurred within 2 years after the operation with rates of 20% and 25.2% for general and epidural patients, respectively. Epidural patients had a 5-year recurrence-free survival of 62.9% versus 70.9% for general patients. Five-year cancer-specific survival was 64.2% and 73.7% for epidural and general patients, respectively.

Retrospective, spinal

Spinal anesthesia for nonmuscle invasive bladder cancer surgery has been found to have a lower recurrence rate when compared with general anesthesia. Koumpan et al. examined 231 patients who underwent transurethral bladder tumor resections, among which 135 received spinal anesthesia and 96 received general anesthesia [16]. They found that spinal anesthesia was associated with a lower recurrence rate when compared to a general anesthesia for nonmuscle invasive bladder cancer. Multivariable patients, who received general anesthesia, had a higher incidence of recurrence (OR 2.06, 95% CI 1.14–3.74, $p = 0.017$) and an earlier time to recurrence (HR 1.57, 95% CI 1.13–2.19, $p = 0.008$) than those who received spinal anesthesia. In a similar study by Choi et al. [17], the five-year tumor recurrence rate following transurethral resection of bladder tumor (TURB) for nonmuscle invasive bladder was significantly lower in the spinal anesthesia group (42%) when compared with the general anesthesia group (53%).

Breast cancer

Breast cancer causes significant morbidity and mortality and is the fifth most common cause of cancer death [47]. Breast cancer is the second most prevalent among all cancers, and over three million women are currently living with a history of breast cancer in the United States [48].

Breast cancer–related deaths usually occur due to metastatic recurrence, and currently, 30%–40% of patients die secondary to metastatic disease [49]. There are multiple different modalities to treat breast cancer including, chemotherapy, endocrine therapy, radiation, and surgical intervention. Surgical removal of the tumor offers the best prospect for a good prognosis, but even with the most skilled surgeons, a mastectomy to remove the primary lesion may disperse malignant cells [50,51]. Although still controversial, it is during the perioperative period that the anesthesiologist may be able to affect the recurrence of metastatic breast cancer.

Prospective studies

Cleveland Clinic is completing a comprehensive investigation of regional anesthesia and breast cancer recurrence, which will include participants from the United States, Ireland, China, Germany, Austria, and Singapore. In this multicenter trial, stage 1–3 patients having mastectomies or isolated lumpectomy with axillary node dissection will be randomly assigned to thoracic epidural or paravertebral anesthesia/analgesia, or general anesthesia and morphine analgesia. Participants will be followed-up for up to 10 years to determine the rate of cancer recurrence or metastasis. Primary outcomes will be cancer recurrence rate, and secondary outcomes will evaluate chronic post-surgical pain in patients receiving paravertebral or thoracic epidural analgesia.

A prospective, multiyear, randomized, triple-masked, placebo-controlled investigation was completed at the University of California San Diego and published in June 2018. Finn et al. evaluated the relationship between cancer recurrence with and without a continuous paravertebral block [52]. Patients included were 60 women over the age of 18 years undergoing a unilateral or bilateral mastectomy with or without axillary lymph node dissection. All patients received ipsilateral or bilateral single-injection thoracic paravertebral blocks(s) with ropivacaine or normal saline. The solution was deposited via perineural catheters, which were placed with ultrasound guidance between third and fourth thoracic vertebrae. The findings of this study showed no evidence that adding a multiple-day, continuous ropivacaine infusion to a single-injection paravertebral block in the immediate postoperative period decreases the risk of postmastectomy cancer recurrence.

Tsigonis et al. published an article in 2016 concerning cure rates for breast cancer in the setting of regional anesthesia [53]. The authors performed a retrospective review of prospectively collected information to identify all stage 0–III breast cancer patients undergoing surgery in a single center. The period ranged from 2001 until 2010 and included 1107 patients: 461 in the general anesthesia group and 646 in the regional anesthesia group. Primary outcomes, which include overall survival, disease-free survival, and local regional recurrence, demonstrated no differences between the general and regional anesthesia groups. Subanalysis, excluding all of stage 0 patients, found the primary outcomes to be similar between the general and regional anesthesia groups. The analysis excluded 69 patients from the general anesthesia group who had both general and regional anesthesia and then included these 69 patients in the regional group rather than the general anesthesia group. Even with these changes, they found no differences in primary cancer outcomes. Propensity-matched patients found no differences in overall survival, disease-free survival, and local regional recurrence between the general and local regional anesthesia groups.

Matsumoto et al. performed a single-center, prospective, randomized controlled study evaluating the potential analgesia benefits of a radical mastectomy with axillary lymph node dissection and breast reconstruction under general anesthesia with and without a combination of serratus anterior plane block with pectoral nerve block I [54]. The study randomized 49 of 182 surgeries for breast cancer between December 2015 and April 2016. One hundred thirty-three cases were excluded because the type of surgical procedure was different from a radical mastectomy with axillary lymph node dissection and breast reconstruction. Matsumoto et al. included secondary outcomes evaluating cytokine response in patients with and without regional anesthesia with a general anesthetic. Cytokines, specifically IL-6 and IL-10, are a vital component of breast carcinogenesis. IL-10 has been used as a prognostic value as an elevated expression is related to recurrence, metastasis, and poor survival in breast cancer. Matsumoto et al. found no differences in IL-6, IL-10, and IL-1 beta levels between general anesthesia and general anesthesia associated with serratus anterior plane block and pectoral nerve block I.

Retrospective studies

In 2006, Exadaktylos et al. demonstrated that women receiving a combination of paravertebral and propofol general anesthesia had a slower time to recurrence when compared with those having general anesthesia with sevoflurane and opioids [55]. The authors concluded a retrospective evaluation of 129 women undergoing breast surgery. This same study found that the rate of recurrence was 6% in patients in the paravertebral and propofol group and 24% in those in the sevoflurane and opioid anesthesia group. This study has several limits, including a retrospective design; the patient population that did not receive a nerve block had relatively larger tumors, smaller margins, and higher chemotherapy rates. It is also important to note that these differences did not reach statistical significance.

Oscar et al. published a review on the impact of regional anesthesia on recurrence, metastasis, and immune response to breast cancer surgery [20]. The authors performed a literature search, finding 467 related articles. From these articles, 15 studies were selected for full text and quality assessment. A meta-analysis was not conducted because of low-quality studies, different staging, and molecular tumor markers in the patients included in each study; different solutions of local anesthetics used for paravertebral blocks; and differences in outcome definitions. Oscar et al. efficiently organized the current literature concerning regional anesthesia and breast cancer recurrence. With regards to paravertebral analgesia (PVB) and breast cancer recurrence, this systematic review found 6 articles, with sample sizes ranging from 60 to 1107 patients. The only published prospective RCT demonstrated no difference in cancer recurrence rates between PVB and placebo. The further 5 studies were retrospective. One found a beneficial effect of PVB, another a negative correlation with PVB, and the remaining found no positive or negative association between PVB and breast-cancer recurrence. The authors concluded that the limited data do not support or refute the use of paravertebral block to reduce cancer recurrence or improve cancer-related survival. There is data supporting the use of paravertebral regional anesthesia to decrease inflammation, prevent immune suppression, and diminish angiogenesis.

Regional anesthesia and gynecological cancers

Gynecological cancers, including cervical and ovarian cancers, are among the most commonly diagnosed cancers in the United States and the world. Epithelial ovarian cancer accounted for approximately 90% of ovarian cancer cases, with 225,000 cases worldwide in 2008 [56]. Nonepithelial ovarian cancers are usually germ cell in origin. They affect younger women and can be effectively treated with chemotherapy [56]. Cervical cancer incidence in the United States is low, with only about 12,000 cases per year [57]. This is due to screening procedures and education on safe sex practices to help prevent the spread of HPV, which is a major risk factor for cervical cancer. Despite these precautions, cervical cancer is the fourth most common cancer worldwide with low- and middle-income socio-economic classes bearing a disproportionate burden of the disease [57]. Studies have shown that the use of local and regional anesthetics combined with general anesthesia during oophorectomy for the treatment of ovarian cancer has positive effects on patient survival and antitumor cytokine activity [58–60]. However, the effects of combined regional and general anesthesia on cervical cancer resection outcomes are less conclusive [61,62].

Prospective studies for ovarian cancer

In a prospective study, Dong et al. randomized 61 patients with epithelial ovarian cancer into two groups for radical resection [60]. The control group received general anesthesia alone, and the study group received general anesthesia with regional anesthesia, along with an epidural. Patients had NK-cell cytotoxicity and cytokines measured both prior to surgery and 4 h post skin incision. Cytokines of interest were IL-1β and IL-8 (tumor-promoting cytokines) and IL-10 and IFN-γ (antitumor cytokines). Both the control and study groups had the same baseline levels of NK-cell cytotoxicity and cytokines, and each group had a decrease in cytokine production at 4 h. The study group, however, had a significantly higher amount of IL-10 and IFN-γ as well as NK-cell cytotoxicity [60]. The combination of general anesthesia and an epidural had better antitumor promoting properties when compared with general anesthesia alone.

Retrospective studies for ovarian cancer

In a single-institution retrospective study, Tseng et al. analyzed long-term survival of patients undergoing primary debulking surgery for advanced ovarian cancer [59]. Of the 648 patients enrolled, 435 received general anesthesia and epidural and 213 received general anesthesia alone. Patient demographics were similar between the two groups. Median progression-free survival (20.8 months with epidural versus 13.9 months without epidural) and overall survival (62.4 months with epidural versus 41.9 months with epidural) were both significantly increased [59]. Furthermore, when accounting for confounding factors such as disease stage and percent of cases with total tumor resection, the control group with only general anesthesia had a 33% increased risk for recurrence/progression rate and a 59% increased risk of death compared to the patients who received both general anesthesia and epidural [59]. A similar retrospective study by Han et al. showed similar survival trends. In patients receiving the epidural, there was a 79.0% 5-year survival rate, whereas patients with only general anesthesia had a 5-year survival rate of 60.5%. These findings were statistically significant. Importantly, the study group also had significantly lower pain 72 h after the operation using the visual analogue scale (VAS) [58].

Prospective study for cervical cancer

A prospective study by Li et al. consisting of 85 cervical cancer patients undergoing a radical resection monitored protumor (IL-1β, IL-6, and IL-8) and antitumor (IL-2 and IFN-γ) cytokines and NK-cell cytotoxicity [62]. Patients in the study group, who received general anesthesia and epidural, had increased NK-cell cytotoxicity, IL-2, and IFN-γ at 4 h and 24 h post skin incision compared to the control group who received only general anesthesia. Similar to the study by Dong et al., Li et al. found that the combination anesthesia promotes antitumor immune activity [62].

Retrospective study for cervical cancer

In a retrospective analysis of 132 patients with cervical cancer undergoing brachytherapy, Ismail et al. found no reduced risk of cancer recurrence or long-term mortality in patients who received combination neuraxial and general anesthesia or general anesthesia alone [61]. Because brachytherapy is not a surgical resection, these results may not be contradictory to those of Li et al. It should be noted that opioid consumption was higher in the general anesthesia alone group. The above two studies regarding the effect of regional anesthesia on cervical cancer outcomes had differing results.

Further study using prospective RCT is necessary to elucidate the potential benefits of local and regional anesthesia in the setting of perioperative immune function and how it relates to gynecological cancer outcomes.

Regional anesthesia and skin and lung cancers

Both preclinical and clinical studies have shown the potential of anesthetics to influence the outcome of cancer patients postoperatively [63]. One such study by Gottschalk et al. investigated the effects of spinal anesthesia and general anesthesia in 273 patients who underwent malignant melanoma resection surgery [64]. In this retrospective analysis, 52 patients received spinal anesthesia and 221 received general anesthesia. Survival between the two groups was not statistically different; however, a trend toward spinal anesthesia providing some benefit for survival was noted (mean survival of 95.9 months for spinal anesthesia and 70.4 months for general anesthesia; $p = 0.087$) [64].

Further prospective analysis is necessary to elucidate whether there is a protective effect of spinal anesthesia on melanoma survival rates. Kofler et al. conducted a prospective study analyzing recurrence and survival rates among patients undergoing regional lymph node dissection for melanoma [65]. A total of 281 patients were enrolled − 162 received general anesthesia and 119 received tumescence local anesthesia (TLA) − with an initial investigation into whether or not TLA can cause tumor cell dissemination. It was found that the rate of lymph recurrence at the site of dissection was 25.3% in the general anesthesia group and 17.6% in the TLA group ($p = 0.082$). A similar trend was noted in the analysis of 10-year survival rates where the general anesthesia group accounted for 56.2% and the TLA group accounted for 67.4% ($p = 0.090$) [65]. Even though these trends are not statistically significant, further prospective studies are needed to fully understand whether or not anesthetic technique has an effect on long-term surgical outcomes of melanoma patients.

In a retrospective cohort study, Lee et al. examined differences in overall and recurrence-free survival in patients who underwent curative resection of primary lung tumors [66]. Patients were divided into groups by postoperative analgesic method, including 574 patients in the patient-controlled analgesia group, 619 patients in the thoracic epidural analgesia group, and 536 patients in the paravertebral block group. There was no difference among the groups in terms of recurrence-free survival; however, a statistically significant increase in the overall survival was found in the paravertebral block group when compared to the other two analgesic methods [66]. One study has shown a difference in lung cancer cells (NCI-H838 cells) motility in the presence of amide-linked versus ester-linked anesthetics [67]. When these cells were dosed with 1-μM ropivacaine and lidocaine, there was a 26% and 21% decrease in cell mobility, respectively, when compared to chloroprocaine [67]. The choice of anesthetic agent can have an effect on cell migration and, therefore, metastasis, potentially affecting the overall survival rate in lung cancer patients. Further study on the effects of anesthesia on the outcomes of lung cancer is needed.

Regional anesthesia and orthopedic cancer

Studies have shown that regional anesthesia can reduce the incidence of cancer recurrence due to the reduced need for opioid administration, its attenuation of the sympathetic nervous system, and its direct antiinflammatory and antitumor properties [18–21]. The administration of opiates and NSAIDs during the perioperative period of orthopedic procedures has been linked with delayed healing and increased inflammation [22–24]. Although data comprising the role opioids may play in the direct promotion of cancer recurrence are inconclusive, several studies have shown that the μ-opioid receptor is involved in tumor progression and even suggested that μ-opioid antagonists may serve as potential antitumor therapies [25,26]. Furthermore, opioids have been shown to produce immunosuppressant effects, which may promote tumor growth and metastasis [27]. In a prospective study of a patient with end-stage osteosarcoma, regional anesthesia reduced pain and, thus, reduced the need for opiates following surgical resection of the growing tumor mass [32].

As regional anesthesia reduces the need for opioids for analgesia following orthopedic procedures, it can indirectly reduce the incidence of orthopedic cancer recurrence [19,37]. The failure of the host immune system presents the key process by which a primary tumor grows and metastasizes [21]. In fact, immunosuppression is correlated with hematologic cancer prognosis, and activation of the immune system has been shown to be protective against tumor development, growth, and metastasis [12,36]. The mechanical trauma associated with orthopedic surgery results in the activation of the sympathetic nervous system, which, in turn, communicates with the immune system to reduce immunosuppression and tumor recurrence [19,36]. In recent years, clinical trials have emphasized the efficacy of immune-modulating therapies for the treatment of osteosarcoma and other bone sarcomas [9]. These studies have demonstrated that activation of NK cells, T lymphocytes, and B cells are cytotoxic to tumor cells [68]. Regional anesthesia has been shown to indirectly activate these lymphocytes through a reduction in catecholamine release, as catecholamines normally suppress the activity of these lymphocytes [69]. Thus, regional anesthesia may indirectly reduce orthopedic cancer recurrence by suppressing catecholamine release. Regional anesthesia can also directly produce antiinflammatory properties that may reduce the incidence of orthopedic cancer recurrence [19,70].

Although numerous studies exist that support the positive effects of regional anesthesia on cancer recurrence, more studies should be conducted to determine the effects of regional anesthesia on orthopedic cancers [18]. The data are likely lacking, as orthopedic oncology procedures often involve the removal of a significant bone and/or muscle and may extend beyond 12 h, thus making general anesthesia more common. However, these upper and lower tumor resections may also be done using regional anesthesia, either alone or in combination with general anesthesia [71]. Therefore, there is potential for future studies to examine the relationship with regional anesthesia and sarcomas. Sarcomas often have a high recurrence rate, and treatment of these bone cancers can be complex [72]. Thus, the identification of improved treatment regimens is needed. As research has already revealed the beneficial effects of regional anesthesia on tumor recurrence and metastasis, further studies should elucidate its potential in reducing the recurrence of orthopedic cancers.

Regional anesthesia and ENT cancer

In the past few years general anesthesia has demonstrated efficacy in reducing ear, nose, and throat cancer recurrence through its ability to inhibit prostaglandins E2 and cyclooxygenase 2 in cancer cells [73]. This is especially important, as prior research has shown that both prostaglandins E2 and cyclooxygenase 2 have been implicated in the development of cervical metastases of squamous cell carcinomas of the head and neck [74,75]. Furthermore, these patients had significantly reduced overall survival rates [75]. Additional research indicated that epidural anesthesia, both alone and in combination with general anesthesia, resulted in a significantly increased overall survival compared to general anesthesia alone in patients undergoing surgery for laryngeal and hypopharyngeal cancer [76].

Bar-Yosef et al. proposed that spinal anesthesia may inhibit cancer progression through attenuation of the neuroendocrine stress via the spinal block [77]. These researchers found a reduced level of NK-cell activity as well as markedly reduced levels of metastasis. Further studies have indicated that although general anesthesia may result in an increased expression of pro-oncogenic protein markers in head and neck squamous cell carcinoma tumor cells, regional anesthesia may differentially affect the expression of these protein markers, thereby providing a potential benefit for cancer patients [78,79]. However, research on the effects of regional anesthesia and ENT cancers is both limited and sometimes contradictory. Cata et al. found that the use of scalp blocks during brain tumor surgery did not significantly increase progression-free survival or overall survival rates in these patients [80]. Despite this finding, scalp blocks have shown better efficacy in reducing pain during neurosurgery, thereby resulting in reduced patient administration of opioids [81]. As increased opioid administration is associated with tumor growth and metastasis, this finding indicates that regional anesthesia may indirectly enhance ENT cancer survival rates [27].

Recent research highlighted which specific types of T cells (i.e., CD103 and CD4) are capable of infiltrating tumor cells in patients with head and neck cancer and consequently increase patient survival by 80% [82]. Research has shown that regional anesthesia activates these T cells and, therefore, may enhance the immunologic response to improve survival rates in these patients [68]. As research has yet to examine the ability of regional anesthesia to alter the levels of these T cells specifically in head and neck cancer patients, further studies should elucidate the potential of regional anesthesia to alter the levels of these lymphocytes in head and neck cancers, as well as the ability of regional anesthesia to alter both recurrence and survival rates in these patients.

Conclusion

Although it is currently unknown what the mechanism behind the antitumor activity of regional anesthesia is, the above studies show the potential treatment benefits and possibility of improved outcomes when regional anesthesia is utilized. These results are important as with the increase in aging population, the incidence of cancer is also rising worldwide and within the United States. If there is potential for the use of regional anesthetics to improve cancer outcomes, it is imperative to both utilize these agents during treatment and understand the mechanism behind their activity. With the relative lack of prospective RCTs regarding the use of regional anesthetics in cancer treatment, further study is necessary before regional anesthetics can be considered for standard of care during surgical resection of cancer tissues.

Practice points

- Surgical resection of primary tumors remains a cornerstone of cancer treatment; however, the surgical process can trigger an immune-suppressing sympathetic response, which promotes tumor growth of any residual cancerous cells post surgery.
- Regional and local anesthesia have become staples of anesthesia and analgesia during and after surgery.
- Recently, a lot of evidence in the form of retrospective and prospective studies has come to light regarding the protective, antitumor properties of anesthetic and analgesic agents across a wide variety of cancers and patient demographics.

Research agenda

- The clinical importance and complete picture regarding the effect of regional anesthesia on cancer recurrence is not currently known due to the paucity of randomized controlled trials (RCTs).
- Although numerous studies exist that support the positive effects of regional anesthesia on cancer recurrence, more studies should be conducted to determine the effects of regional anesthesia on orthopedic cancers.
- There is a lack of good-quality, prospective RCTs examining the effectiveness of epidural analgesia in improving colon cancer survival and reducing cancer recurrence.
- There are very few studies evaluating the use of regional anesthesiology in hepatocellular cancer.

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