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REVIEW

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Influence of perioperative anesthesia methods or anesthetic agents preferred for gastric cancer surgery on the survival of patients: a narrative review

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Abstract

Background: Gastric cancer is a major global public health problem. It is the fourth most common cancer and the second cause of cancer-related deaths worldwide. Despite advances in the field of medical and radiation oncology, surgical resection is a crucial intervention and remains the mainstay of gold standard treatment. Recently, the effects of anesthesia method(s) and/or anesthetic agent(s) on survival for different types of cancers gained attention. So, we want to summarize the evidences of anesthesia methods and/or anesthetic agents preferred for gastric cancer surgery on the survival.

Main body: The Web of Science software was used for the search and the analysis. To analyze scientific productivity of all scientific papers published about survival of patients due to the anesthesia methods or anesthetic agents on gastric cancer in Science Citation Index Expanded (SCI-E) from 1980 to December 5, 2020, the date of the search was searched by using the terms of "gastric cancer," "survival," and "anesthesia" in the topic search section of the software.

As a result, overall, fifteen papers were related to our topic. Four of these studies compared total intravenous anesthesia (TIVA) with general anesthesia, five of these compared general anesthesia with general anesthesia combined with epidural anesthesia/analgesia for gastric cancer, and three of these studies investigated effect of anesthetic agents for gastric cells in in vitro conditions. Other publications were review on this topic.

Conclusions: The important role of anesthesia in treatment of gastric cancer patients is still controversial. Further prospective randomized studies are needed.

Keywords: Anesthesia, Anesthetic drugs, Computer software application, Gastric cancer, Survival, General anesthesia

Background

Gastric cancer (GC) is a major global public health problem (Pei et al. 2020; Jiang et al. 2017). It is the fourth most common cancer (Huang et al. 2020; Oh et al. 2019; Yang et al. 2016) and the second cause of cancer-related deaths worldwide (Oh et al. 2019; Yang et al. 2016; Dan et al. 2018; Zheng et al. 2018). Despite advances in the field of medical and radiation oncology (Hong et al. 2019), surgical resection is crucial intervention and remains the mainstay of gold standard treatment (Pei et al. 2020; Huang et al. 2020; Oh et al. 2019; Yang et al. 2016; Zheng et al. 2018; Hong et al. 2019; Wang et al. 2017). Recently, the effects of anesthesia method(s) and/or anesthetic agent(s) on survival for different types of cancers gained attention (Pei et al. 2020). Numerous anesthetic agents and different anesthesia approaches (general anesthesia,

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total ıntravenous anesthesia, epidural anesthesia/analgesia) applied for management of gastric cancer during surgery (Huang et al. 2020) and in vitro studies for anesthetic agents have been evaluated on tumor recurrence, metastasis, and survival for gastric cancer (Pei et al. 2020; Huang et al. 2020; Hong et al. 2019), but the outcomes were controversial (Oh et al. 2019). Furthermore, factors affecting cancer prognosis are very diverse and complex, and they may not differ simply because of the anesthetic used (Hong et al. 2019). On the other hand, studies on the survival of patients due to the anesthesia methods or anesthetic agents on gastric cancer is so limited (Wang et al. 2017). So, we want to summarize the evidences of anesthesia methods and/or anesthetic agents preferred for gastric cancer surgery on the survival.

Methods

The aim of this narrative review was to analyze the publications on the effect of anesthesia methods or anesthetic agents on gastric cancer; the Web of Science (WoS) software was used. To analyze scientific productivity of all scientific papers published about survival of patients due to the anesthesia methods or anesthetic agents on gastric cancer in Science Citation Index Expanded (SCI-E) from the 1980 to December 5, 2020, the date of the search was searched by using the terms of "gastric cancer," "survival," and "anesthesia" in the topic search section of the software. We encountered 34 papers that are related to our terms in WoS software. We further investigated these papers one by one, and we discovered that 15 papers were related to our topic. Then, we summarized these publications according to in vivo and in vitro publications. Then, we summarized the in vivo studies according to anesthesia types: general anesthesia or total intravenous anesthesia or anesthesia method that was combined with regional anesthesia or analgesia.

Results

Overall, fifteen papers were related to our topic. Four of these studies compared total intravenous anesthesia (TIVA) with general anesthesia (Table 1), five of these compared general anesthesia with general anesthesia combined with epidural anesthesia/analgesia for gastric cancer (Table 2), and three of these studies investigated effect of anesthetic agents for gastric cells in in vitro conditions (Table 3). All these are summarized in tables. Two publications are on "Outcomes of regional anesthesia in cancer patients" and on "Importance of anesthesia in multimodal oncologic therapeutical concepts." And the last work is review and summarize the published literature regarding the preclinical research methods and findings on the influence of local anesthetics on cancer cells.

Discussion

In recent decades, scientists have focused on the effects of perioperative factors and interventions on cancer recurrence and overall survival. These factors include tumor type, tumor stage and size, surgical skill and techniques, anesthetic technique, radiotherapy with or without chemotherapy, blood loss, transfusions during the perioperative period, and comorbid diseases (hypertension, immunodeficiency, diabetes, or chronic obstructive pulmonary disease) (Wang et al. 2016). Clinical events such as tissue injury, pain, general anesthesia, blood transfusion, and opioid drugs may lead to alteration of immune response after surgical trauma. The activation of multiple biological cascades [hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS)] due to these clinical events leads to postoperative immunosuppression by affecting both humoral and cell-mediated responses (Wang et al. 2017).

General anesthesia and epidural anesthesia/analgesia are commonly applied anesthesia method(s) for gastric cancer surgery (Pei et al. 2020). So, anesthetics are unavoidable for gastric cancer patients to facilitate the surgery during surgical treatment (Jiang et al. 2017). And recently, there is evidence to suggest that anesthetic techniques and anesthetic drugs may potentially have a role in tumor recurrence/metastasis (Jiang et al. 2017; Yang et al. 2016). Therefore, anesthesia has an important impact on cancer development by the choice of drugs and method of anesthesia and/or analgesia (Yang et al. 2016; Shin et al. 2017; Weitz et al. 2006). However, the mechanism by which these anesthetics affect tumor metastasis remains poorly understood (Jiang et al. 2017). Each anesthetic technique/agent has its unique effect on immune regulation and cancer growth factor production (Hong et al. 2019). One of the most widely used intravenous anesthetic agent during cancer resection surgeries is propofol (2,6-diisopropylphenol) (Yang et al. 2016; Hong et al. 2019). According to results of the investigations, propofol not only has anesthetic properties but also has antitumor effects. Probable mechanisms for antitumor effect of propofol are inhibition of proliferation (Yang et al. 2016; Zheng et al. 2018), invasiveness (Yang et al. 2016; Zheng et al. 2018), adhesion (Yang et al. 2016), tumor recurrence, and metastasis (Zheng et al. 2018), inhibitor role in the growth and survival of gastric gastric cancer cells (Jiang et al. 2017; Yang et al. 2016; Zheng et al. 2018; Hong et al. 2019), inducing apoptosis of cancer cells (Yang et al. 2016), and stimulation of activation and differentiation of T-helper lymphocytes (Zheng et al. 2018). In a study, authors reported that propofol exhibits better immunomodulatory properties than volatile anesthetics (Hong et al. 2019). In another study, authors stated that sevoflurane exhibited immunosuppression

Table 1 Summary of studies on gastric cancer that compare TIVA with GA

Study (author/year)	Method	Intervention	Anesthesia methods and/or anesthetic agents	Notes
(Huang et al. 2020)	Retrospective	TIVA vs GA (none of the patients had epidural catheter)	**TIVA (*n* = 190)** Ind = propofol + fentanyl + lidocaine 2% + rocuronium Man: propofol infusion + fentanyl (repetitive bolus) + cisatracurium (repetitive bolus) **GA (*n* = 218)** I = propofol + fentanyl + lidocaine + rocuronium or succinylcholine M: desflurane + fentanyl (repetitive bolus) + cisatracurium (repetitive bolus)	TIVA improved survival and reduced the risk of recurrence and metastasis during the 5-year follow-up
(Hong et al. 2019)	Retrospective	TIVA vs GA (5 major types of surgery evaluated) (breast, colon, liver, lung, stomach)	**TIVA (*n* = 903)** I = propofol + remifentanil M: propofol infusion + remifentanil infusion **GA (*n* = 1304)** I = propofol/etomidate + remifentanil M: remifentanil/N20 + (desflurane/sevoflurane/isoflurane)	There were no differences 5 years overall
(Oh et al. 2019)	Retrospective cohort	TIVA vs GA (none of the patients had epidural catheter)	**TIVA (*n* = 769)** I = propofol + remifentanil M: propofol infusion + remifentanil infusion **GA (*n* = 769)** I = remifentanil + (desflurane/sevoflurane) M: remifentanil + (desflurane/sevoflurane)	Propofol-based TIVA was not significantly associated with decrease in the 1-year overall or cancer-related mortality
(Zheng et al. 2018)	Retrospective observational study	TIVA vs GA	**TIVA (*n* = 897)** I = midazolam + propofol + fentanyl M: propofol infusion + remifentanil infusion Postoperative analgesia: IV PCA (fentanyl or sufentanil) **GA (*n* = 897)** I = midazolam + propofol + fentanyl M = sevoflurane + remifentanil infusion Postoperative analgesia: IV PCA (fentanyl or sufentanil)	TIVA may be associated with improved survival

and tumorigenesis through a number of mechanisms (Zheng et al. 2018). Another study reported the role of desflurane as an antitumor agent especially in gastric cancer is still controversial (Wang et al. 2016).

So, some authors compared TIVA with general anesthesia (alone) for survival after gastric cancer surgery in the literature. However, results reported on this issue are still contradictory. While Huang et al. (Huang et al. 2020) and Zheng et al. (Zheng et al. 2018) reported improved survival with TIVA, Hong et al. (Hong et al. 2019) and Oh et al. (Oh et al. 2019) stated no difference in 5 years and 1 year overall respectively.

The neuraxial techniques (anesthesia/analgesia) that are applied during cancer surgeries may improve the prognosis after cancer surgery, were first emerged approximately a decade ago, and were met by genuine enthusiasm of the anesthesia society (Shin et al. 2017). In a study, the authors stated that the proposed mechanisms for this can be summarized as "immunomodulation" and "anti-inflammation" (Shin et al. 2017; Liu et al.

Table 2 Summary of studies on gastric cancer that compare GA with GA combined with epidural anesthesia/analgesia

Study (author/year)	Method	Intervention	Anaesthesia methods and/or anesthetic agents	Notes
(Pei et al. 2020)	Retrospective	GA vs EGA	**GA (*n* = 97)** Anesthetic agents (no information) **EGA (*n* = 97)** Anesthetic drugs (no information) **(patients were matched according to the propensity score)**	EGA did not show a significant reduction in the incidence of recurrence and/or metastasis
(Wang et al. 2019)	Retrospective randomized observer blinded study	GA vs EGA	**GA (*n* = 25)** I = midazolam + propofol + sufentanil + cisatracurium M = propofol + remifentanil infusion Postoperative analgesia: IV PCA (sufentanil) **EGA (*n* = 25)** I = midazolam + propofol + sufentanil + cisatracurium M = propofol + epidural PCA (ropivacaine + sufentanil) Postoperative analgesia: epidural PCA (ropivacaine + sufentanil)	EGA decreases immunosuppression gastric cancer resection
(Wang et al. 2017)	Retrospective	GA vs EGA	**GA (*n* = 2856)** I = midazolam + propofol + fentanyl M = (propofol/sevoflurane) + (remifentanil infusion/fentanyl) Postoperative analgesia: IV PCA (sufentanil or fentanyl) **EGA (*n* = 1362)** I = anesthetic drugs (no information) M = anesthetic drugs (no information) + epidural anesthesia (ropivacaine/levobupivacaine infusion) Postoperative analgesia: epidural PCA (ropivacaine/levobupivacaine + fentanyl)	EGA and epidural PCA may be associated with the improved overall survival
(Wang et al. 2016)	Retrospective	GA vs EGA	**GA (*n* = 116)** I = midazolam + propofol + sufentanil M = propofol + remifentanil infusion **EGA (*n* = 157)** I = midazolam + propofol + sufentanil M = propofol + epidural anesthesia (ropivacaine or levobupivacaine infusion)	EGA had no effect on the long-term survival, but younger patients who received EGA were more likely to have longer survival
(Shin et al. 2017)	Retrospective	Epidural analgesia (PCA) vs IV analgesia (PCA)	**GA with IV PCA (*n* = 374)** I = anesthetic agents (no information) M = remifentanil + sevoflurane + N20 Postoperative analgesia: IV PCA (fentanyl) **EGA with epidural PCA (*n* = 3425)** I = anesthetic agents (no information) M = remifentanil + (enflurane/isoflurane) + N20 Postoperative analgesia: epidural PCA (ropivacaine + fentanyl)	Postoperative use of epidural analgesia was not found to be associated with reduced recurrence or mortality

Table 3 Summary of studies on gastric cancer cells with anesthetic agents in in vitro conditions

(Jiang et al. 2017)	In vitro	Effect of muscle relaxant anesthetics on growth, migration, and invasion	Cell culture + rocuronium bromide Cell culture + vecuronium bromide Cell culture + cisatracurium besilate	Rocuronium bromide acts as a stimulant of gastric cancer cell growth, migration, and invasion in vitro
(Yang et al. 2016)	In vitro	Effect of propofol on growth and survival of gastric cancer cells	Cell culture + propofol treatment (cell viability, migration and invasion assay, flow cytometry, quantitative real-time PCR, Western blot analysis)	Propofol inhibits gastric cancer cell growth and induces cell apoptosis
(Dan et al. 2018)	In vitro	Effect of local anesthetic bupivacaine on gastric cancer	Cell culture + bupivacaine (measurement of proliferation and apoptosis, Boyden chamber migration assay, measurement of oxygen consumption rate, measurement of mitochondrial respiratory complex activity and ATP level, measurement of RhoA activity)	Bupivacaine has direct anticancer activity with the dominant inhibitory effects on gastric cancer migration rather than growth and survival

2020). Other probable mechanism(s) that the many studies reported on this subject are as follows: decrease in intra- and postoperative neuroendocrine stress responses (Pei et al. 2020; Wang et al. 2017; Wang et al. 2016; Wang et al. 2019; Liu et al. 2020), reduce in opioid exposure (Wang et al. 2017; Liu et al. 2020) that leads to immunosuppression (Oh et al. 2019; Wang et al. 2017; Liu et al. 2020), reduce in cytokines (Wang et al. 2019), prevention of surgery and anesthesia-related immunosuppression (Pei et al. 2020), antiangiogenesis (Liu et al. 2020), and improvement in the function of T lymphocytes (Wang et al. 2019).

The studies have focused on comparing general anesthesia alone with general anesthesia combined with epidural analgesia. Although Wang et al. reported improvement in overall survival in their three studies in 2016 (Wang et al. 2016), 2017 (Wang et al. 2017), and 2019 (Wang et al. 2019), respectively, Pei et al. (Pei et al. 2020) and Shin et al. (Shin et al. 2017) showed no significant reduction in the incidence of recurrence and/or metastasis and mortality.

Although a decade have passed after the first emerged hypothesis (Shin et al. 2017), the studies on the effect of epidural anesthesia on overall survival of patients or the recurrence of cancer with gastric cancer is still presenting conflicting results on the hypothesis (Wang et al. 2016; Shin et al. 2017; Wang et al. 2019).

In another study, authors dealt with muscle relaxants which are widely used in the induction and maintenance of anesthesia management accepted as adjunctive drug in anesthesia management. They stated that there is little research on the effect of muscle relaxants on tumor metastasis (Jiang et al. 2017). They searched the impact of muscle relaxants on breast cancer metastasis in 2016. Interestingly, they reported that rocuronium bromide promoted breast cancer cell growth, migration, and invasion, but vecuronium bromide did not (Jiang et al. 2016). So, they planned to investigate the effects of muscle relaxants on gastric cells in in vitro conditions, and they stated that Rb is a stimulant of gastric cancer cell growth, migration, and invasion *in vitro*. They suggested to use vecuronium bromide and cisatracurium besilate in gastric cancer surgery (Jiang et al. 2017).

Not only anesthetic/analgesic agents and muscle relaxants but also local anesthetics (Liu et al. 2020; Cata 2018) and labetalol and nonselective β-adrenergic antagonists (Shin et al. 2017) may effect the cancer cells. Lidocaine, the local anesthetic that can be applied intravenously, does not always have the most potent anticancer effect in in vitro studies. But authors suggest to develop a new intravenous local anesthetic with high anticancer potency with low toxicity (Liu et al. 2020). Interestingly, authors stated that labetalol and nonselective β-adrenergic antagonists were associated with greater mortality after gastrectomy (Shin et al. 2017).

In addition to all these, performing gastric surgery by laparotomy versus laparoscopic surgery is an other important factor for survival. Laparoscopic surgery induces less surgical stress and decreases the inflammatory response when compared with laparotomy (Oh et al. 2019).

Limitation of this study was all clinical studies evaluated in this narrative review were retrospective.

Conclusions

In view of the above, the important role of anesthesia in treatment of gastric cancer patients is still controversial. Further prospective randomized studies are needed.

Abbreviations

SCI-E: Science Citation Index Expanded; TIVA: Total intravenous anesthesia; GC: Gastric cancer; WoS: Web of Science; HPA: Hypothalamic-pituitary-adrenal axis; SNS: Sympathetic nervous system.

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FY and KB reviewed the available literature, prepared the study design, reviewed and edited the final manuscript, and approved the final manuscript. The authors read and approved the final manuscript.

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Declarations

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Ethical committe approval was not necessary for this study.

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Competing interests
The authors declare that they have no competing interests.

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