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Is There Any Difference of Anesthesia Methods or Anesthetic Agents Preferred for Gastric Cancer Surgery on the Survival of Patients: A Narrative Review

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ABSTRACT

Introduction: 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 crucial intervention and remains the mainstay the 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.

Material-method: Web of Science software was used for the search and the analysis. To analyse 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 5th, 2020; the date of the search, were searched by using the terms of “gastric cancer”, “survival” and “anesthesia” in the topic search section of the software.

Results: Overall fifteen papers were related to our topic. Four of these studies compared TIVA with general anesthesia; five of these compared general anesthesia with general anesthesia combined with epidural anesthesia/analgesia for gastric cancer, three of these studies investigated effect of anesthetic agents for gastric cells in *in vitro* conditions. Other publications were review on this topic.

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

Key words: gastric cancer, survival, anesthesia, Web of Science software

Introduction: Gastric cancer (GC) is a major global public health problem (1,2). It is the fourth most common cancer (3-5) and the second cause of cancer-related deaths worldwide (4-7). Despite advances in the field of medical and radiation oncology (8), surgical resection is crucial intervention and remains the mainstay the gold standard treatment (1,3-5,7-9). Recently, the effects of anesthesia method(s) and/or anesthetic agent(s) on survival for different types of cancers gained attention (1). Numerous anesthetic agents and different anesthesia approaches (general anesthesia, total intravenous anesthesia, epidural anesthesia/analgesia) applied for management of gastric cancer during surgery (3) and *in vitro* studies for anesthetic agents have been evaluated on tumor recurrence, metastasis and survival for gastric cancer (1,3,8); but the outcomes were controversial (4). Furthermore factors affecting cancer prognosis are very diverse and complex and they may not differ simply because of the anesthetic used (8). On the other hand studies on the survival of patients due to the anesthesia methods or anesthetic agents on gastric cancer is so limited (9). So we want to summarize the evidences of anesthesia methods and/or anesthetic agents preferred for gastric cancer surgery on the survival.

Material-method: Web of Science (WoS) software was used for the search and the analysis. To analyse 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 5th, 2020; the date of the search, were searched by using the terms of “*gastric cancer*”, “*survival*” and “*anesthesia*” in the topic search section of the software. We encountered 34 papers that 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.

Results: Overall fifteen papers were related to our topic. Four of these studies compared 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), 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) (10). Clinical events such as tissue injury, pain, general anesthesia, blood transfusion and opioid drugs may lead to alteration of immun 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 (9).

General anesthesia and epidural anesthesia/analgesia is commonly applied anesthesia method(s) for gastric cancer surgery (1). So anesthetics are unavoidable for gastric cancer patients to facilitate the surgery during surgical treatment (2). And recently there is evidence to suggest that anesthetic techniques and anesthetic drugs may potentially have a role in tumor recurrence/ metastasis (2,5). Therefore, anesthesia has an important impact on cancer development by the choice of drugs and method of anesthesia and/or analgesia (5,11,12). However, the mechanism by which these anesthetics affect tumor metastasis remains poorly understood (2). Each anesthetic technique/agent has its unique effect on immune regulation and cancer growth factor production (8). One of the most widely used intravenous anesthetic agent during cancer resection surgeries is propofol (2,6-diisopropylphenol) (5,8). According to results of the investigations, propofol has not only anesthetic properties but also has antitumor effects. Probable mechanisms for antitumor effect of propofol are

inhibition of proliferation (5,7), invasiveness (5,7), adhesion (5), tumor recurrence and metastasis (7); inhibitor role in the growth and survival of gastric cancer cells (2,5,7,8); inducing apoptosis of cancer cells (5) and stimulation of activation and differentiation of T-helper lymphocytes (7). In a study authors reported that propofol exhibits better immunomodulatory properties than volatile anesthetics (8). In another study authors stated that sevoflurane exhibited immunosuppression and tumorigenesis through a number of mechanisms (7). Another study reported the role of desflurane as an antitumor agent especially in gastric cancer is still controversial (10).

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 (3) and Zheng et al (7) reported improved survival with TIVA; Hong et al (8) and Oh et al (4) stated no difference in 5 year and 1 year overall respectively.

The neuraxial techniques (anesthesia/analgesia) that applied during cancer surgeries may improve the prognosis after cancer surgery, was first emerged approximately a decade ago, and was met by genuine enthusiasm of the anesthesia society (11). In a study the authors stated that the proposed mechanisms for this can be summarized as “immunomodulation” and “anti-inflammation” (11,15). Other probable mechanism(s) that the many studies reported on this subject are: decrease in intra- and postoperative neuro-endocrine stress responses (1,9,10,13,15), reduce in opioid exposure (9,15) that leads to immunosuppression (4,9,15), reduce in cytokines (13), prevention of surgery and anesthesia related immunosuppression (1), antiangiogenesis (15) and improvement in the function of T lymphocytes (13).

Then 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 (10), 2017 (9) and 2019 (13) respectively; Pei et al (1) and Shin et al (11) showed no significant reduction in the incidence of recurrence and/or metastasis and mortality.

Although a decade have passed after the first emerged hypothesis (11), 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 (10,11,13).

In another study, authors dealt with muscle relaxants which are widely used in the induction and maintenance of anesthesia management as accepted as adjunctive drug in anesthesia management. They stated that there is little research on the effect of muscle relaxants on tumor metastasis. So they investigated the effects of muscle relaxants on gastric cells in *in vitro* conditions and reported that muscle relaxants impact on tumor metastasis is critical (2).

Not only anesthetic/analgesic agents and muscle relaxants but also local anesthetics (14,15) and labetolol and non-selective β adrenergic antagonists (11) may effect the cancer cells. Lidocaine, the local anesthetic that can be applied intravenously does not always have the most potent anti-cancer effect in *in vitro* studies. But authors suggest to develop a new intravenous local anesthetic with high anti-cancer potency with low toxicity (14). Interestingly authors stated that labetolol and non-selective β adrenergic antagonists were associated with greater mortality after gastrectomy (11).

In addition to all these, performing gastric surgery by laparotomy versus laparoscopic surgery is other an important factor for survival. Laparoscopic surgery induces less surgical stress and decreases the inflammatory response when compared with laparotomy (4).

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

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