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Original Research Article

Effect of regional versus general anaesthesia on postoperative opioid consumption, clinical outcomes and cognitive function in Chinese patients undergoing metastatic cancer surgery

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Abstract

Purpose: *To compare postoperative opioid consumption, inflammatory biomarkers, cognitive function and safety profile of regional anesthesia (RA) versus general anesthesia (GA) in Chinese patients undergoing metastatic cancer surgery.*
Method: *Chinese patients undergoing metastatic cancer surgery were enrolled and received either RA or GA) in allocation ratio of 1:1. The following efficacy variables were assessed: 1) pain score was measured on VAS scale; 2) post-operative consumption; 3) inflammatory biomarkers; 4) cognitive function; 5) clinical outcomes. Safety was also assessed.*
Results: *Data for a total of 220 patients were analyzed. Compared to GA alone, the combination of RA and GA demonstrated significantly greater reduction in post-operative pain with decreased postoperative opioid consumption. Also, RA/GA combination inhibited inflammatory response when compared to patients who received GA only, indicating that RA + GA improved immune response in patient undergoing surgical intervention. The severity of signs and symptoms of dementia were similar at baseline visit ($p > 0.05$). Patients of RA/GA group had significantly greater relief in signs and symptoms of dementia/cognitive impairment, when compared to the GA-treated patients ($p < 0.05$). However, incidence of complications (including adverse events) was comparable for both groups ($p > 0.05$). Additionally, RA/GA was also associated with shorter length of hospital stay, compared to GA.*
Conclusion: *RA/GA combination demonstrates significantly greater improvement in the level of clinical outcomes, decreases postoperative opioid consumption, and improves cognitive functions when compared to GA in Chinese patients undergoing metastatic cancer surgery.*

Keywords: *Regional anesthesia, General anesthesia, Epidural, Metastatic cancer surgery, Cognitive function, Inflammatory response, Postoperative opioid consumption*

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INTRODUCTION

Metastatic cancer is one of the leading causes of mortality worldwide, that add huge financial burden to patients and their families [1,2]. The patients who had solid organ cancer often requires surgical intervention, however, some extent of tumor spread is inevitable [2,3]. During

surgical intervention, skin injury affects modulation of several inflammatory biomarkers such as cytokines, which causes inflammatory reactions, which greatly influence the efficacy of treatment and cause poor prognosis including overall survival [1-4].

It has been reported that surgical intervention causes surgical stress response and immunosuppression, which negatively impact the efficacy of anti-cancer drugs and cause severe impact on survival outcome and increase mortality cases among patients with metastatic cancer. A study reported that increase level of inflammatory biomarkers such as cytokines increases immunosuppressive properties, that results in tumor relapse and metastasis, that substantially reduced the survival period of cancer patients. Thus, controlling inflammatory reactions and protecting immune function during perioperative period is essential to achieve targeted therapeutic response in cancer patients [1-6].

Another complication after surgical intervention was cognitive impairment that lasts for weeks or several months. It again affects patient's life negatively by affecting their quality of life and add burden to their family members. Physiologically two receptors namely $GABA_A$ and NMDA are known to play important role in cognitive impairments [7]. During surgical intervention, several pain management options are available such as patient-controlled analgesia (PCA), regional anesthesia are more commonly used to manage post-operative pain [8-11]. Opioid analgesics, as PCA, such as morphine and other derivatives, are the most frequently used primary treatment analgesia in patients undergoing major surgical intervention such as cancer surgery. However, the use of Opioids PCA are commonly associated with adverse events such as sedation, nausea/vomiting, and pruritus. The use of regional anesthesia (RA) has been popular in recent years. Recently a new technique called femoral nerve blocks (FNB), a type of RA has been introduced, that reduces the requirement of opioids post-operatively in patients who underwent major surgical intervention [8-15].

There is no study is evaluating the effect of RA versus general anesthesia (GA) on postoperative opioid consumption, inflammatory biomarkers, cognitive function in Chinese patients undergoing metastatic cancer surgery. There is also unavailability of clinical data on usage of RA versus GA in Chinese population undergoing surgical intervention for metastatic cancer surgery. Thus, the present study was designed to compare postoperative opioid consumption, inflammatory biomarkers, cognitive function and safety profile of RA versus GA in Chinese patients undergoing metastatic cancer surgery.

METHODS

Patients and ethics

Chinese patients diagnosed with any metastatic stage of cancer undergoing surgical intervention were explained the study procedures, role and responsibility of subject and investigator, then enrolled at study site after obtaining their written inform consent form. The study commenced only after receiving written approval from ethics committee. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, applicable laws and regulations. To assess the eligibility criteria, each patient was subjected to screening visit, where blood samples for complete laboratory assessment as well as chest x-ray, and electrocardiogram to confirm the suitability of subject was done.

Patients with American Society of Anesthesiologists (ASA) score of ≥ 4, had history of bleeding disorder, uncontrolled diabetes, heart disease, mental disorder, chronic renal disease, sleep disorder, pleural adhesions, and underwent ipsilateral thoracic surgery were excluded. Also, patients with deformity in airways or spinal, or chest wall were also excluded. The patients with any other pathology, which consulting physician or doctor feels may affect the outcome of the study or patients who were receiving prohibited concomitant medications or undergoing any other surgery were excluded.

Treatments and study procedure

Subjects who met eligibility criteria were enrolled and received either reginal anesthesia combined with general anesthesia (group RA + GA) or general anesthesia (group GA) in allocation ratio of 1:1. Intravenous fentanyl was administered to all patients as pre-anesthetic medication.
In the RA group, an epidural catheter was inserted between L1 an L2 using the median/loss-of-resistance approach. Lidocaine (2 %) up to 3 mL as test dose was administered using epidural catheter after getting negative aspiration results of blood and cerebrospinal fluid. Then a second dose of ropivacaine (0.7 %) in 6 – 8 mL was administered via epidural catheter. Ropivacaine (0.7 %, 5 mL) was administered every 1 h during surgery. All patients received sevoflurane and analgesic as a part of maintenance of anesthesia. In the GA

group, propofol (IV injection, 1 to 2 mg per kg), fentanyl (3 µg/kg), and rocuronium (0.6 mg/kg) were used to induce general anesthesia. Ventilator was administered with tidal volume of up to 8 mL/kg and body temperature was maintained normal.

Ondansetron was administered as prophylaxis treatment to prevent nausea and vomiting. All patients received patient-controlled analgesic after the end of surgery. Each patient received opioid analgesia using PCA pump, in which morphine 40 mg mixed in 250 mL of saline solution, and administered to patients as and when required. After the surgical procedure, pain score on VAS scale was measured.

The following efficacy variables were assessed: Pain score was measured on VAS scale (0 - 10 scale) immediately after exiting from OT room, and at 3, 6, 12, 24, 48 and 72 h. The pain scope was assessed by a blind observer. Also, blood sample from each patient was taken before administration of anesthesia (baseline), 2, 24, 48 and 72 h after surgery to measure inflammatory biomarkers. Moreover, cognitive function of each patient was evaluated before and after the anesthesia using scales such as SIB (0 - 100 score, lower: severe impairment, higher score: less impairment), CIBIC functional status scale (lower: higher improvement, higher score: lower improvement), ADCS-ADL daily living score and MMSE (0 - 54 score, lower: severe impairment, higher score: less impairment). Other key variables assessed were: opioid consumption, length of hospital stay, treatment satisfaction as measured using degree of pain control (using 5-point Likert scale), and post-operative complications, blood loss, incidences of hypotension, and cardiopulmonary stability during surgery. Safety was assessed throughout the study period. Also, survival outcome measured in both groups was assessed after discharge. Each patient was followed up for at least 3 years after discharge.

Determination of inflammatory cytokines

After 12 hours of fasting, blood sample was collected, and blood samples were centrifuged at + 4 °C, with 1000 g for 10 minutes. Interleukin-1 (IL-1) and Interleukin-8 (IL-8) levels were analyzed by “Immulite 2000” immunassay analyzer (Siemens Healthcare Diagnostics, USA). Tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) were measured by ELISA kits (ELX 50) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA).

Evaluation of CD3, CD4 and CD8

Five microliters of monoclonal antibody (human leukocyte differentiation antigens of CD3, CD4 and CD8) was added to fifty microliters of a blood sample and hatched for 15 min at 25 °C. Then, the erythrocytes were lysed using OptiLyse C (100 µL) and sample was kept aside for 10 min. Chemical reaction was terminated using phosphate buffer (250 µL). The samples were analyzed by flow cytometry using Cytomics FC 500 and CXP software (Beckman Coulter).

Statistical analysis

Since, the present study was designed as pilot or preliminary investigation, there was no formal calculation of sample size required. This present preliminary investigation planned to recruit at least 100 Chinese patients with metastatic cancer undergoing major surgery in each treatment group. The finding of the present study may benefit the scientific community and may help to design large clinical trial across the globe. Quantitative data were analyzed using t test or Mann Whitney based on the normality of the data. Categorical data were analyzed using chi-square/fisher exact test as appropriate considering the data size. KM curve was used to compare survival outcome of both groups.

RESULTS

A total of 220 Chinese patients with metastasis cancer were enrolled after satisfying all the eligibility criteria. All the enrolled Chinese patients completed the study as per the study protocol. Patient characteristic is presented in table 1. Demography and baseline characteristic between both groups were found to be similar. As indicated in Figure 1, the patients of both treatment groups had greater reduction in post-operative pain score at each time point. However, reduction in VAS score was significantly greater in patients who received RA when compared to patients who received GA. At early time points, pain score after was significantly lower in patients who received RA as compared to general anesthesia alone. Similar trend of results was found after 48 and 72 h of treatment (Figure 1). This indicates that RA demonstrates significantly greater reduction in postoperative pain as compared to GA. This was further confirmed by postoperative opioid consumption, which was significantly lower in patient who received RA as compared to general anesthesia from day 1 to 4 (Figure 1). Postoperative opioid consumption was significantly higher in patients that received combination of epidural and general anesthesia

as compared to general anesthesia (Figure 2). As indicated in Figure 2, the patients of both treatment groups had greater reduction in postoperative opioid consumption at each time points. However, reduction in postoperative opioid consumption was significantly greater in patients who received RA when compared to patients who received GA. At early time points, postoperative opioid consumption after was significantly lower in patients who received RA as compared to GA. Similar trend of results was found after 48 and 72 h of treatment (Figure 2). This indicates that RA demonstrates significantly greater reduction in postoperative opioid consumption as compared to GA.

Moreover, number of doses of diclofenac taken post-operatively was significantly higher among patients receiving GA when compared to patients receiving RA (Table 2). The length of hospital stay was also significantly longer in patients received GA as compared to RA (Table 2). In addition, degree of pain control satisfaction was higher in patients receiving RA as compared to GA.

Table 1: Patient characteristic

Variable	RA (N=110)	GA (N=110)	P value
Age (years)	54.2 (2.1)	58. 3 (3.2)	>0.05
Weight, kg	66.2 (2.2)	64.1 (3.6)	>0.05
BMI (kg/m^2)	26.7 (2.3)	25.6 (2.1)	>0.05
Gender (M/F), %	80/20	70/30	>0.05
ASA class, %			
I	20	30	>0.05
II	40	35	
II	40	35	
Tumor size, cm	2.3 (1.6)	3.5 (1.3)	>0.05
Anesthesia time (min)	286.13 (12.1)	346.23 (14.1)	>0.05
Surgical time (time)	281.3 (12.3)	241.2 (31.3)	>0.05
Stage			
I	80	75	>0.05
II	10	15	>0.05
IIa	10	10	>0.05
SIB	68.8 (2.1)	70.2 (1.8)	>0.05
ADCS-ADL	78.6 (10.2)	73.2 (11.3)	>0.05
CIBIS+/CIBIC	66.6 (12.1)	77.2 (12.1)	>0.05
MMSE	73.6 (13.2)	75.2 (11.4)	>0.05
Baseline cognitive score	82.1 (1.2)	80.1 (1.2)	>0.05

Values expressed as mean (SD) for numerical variable, % of patients reported for categorical variables

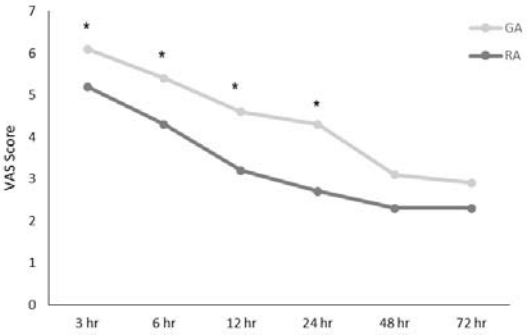

Figure 1: Comparison of RA and GA in terms of reduction in post-operative pain score using VAS scale. *P < 0.05 compared to reference, otherwise difference was not statistically significant (using unpaired test)

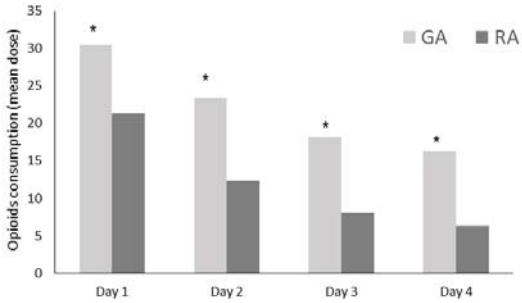

Figure 2: Comparison of opioids consumption post-operatively in patients treated with RA and GA. *P < 0.05 compared to reference (using unpaired test)

Table 2: Comparison of RA and GA for clinical outcomes

Variable	RA (N=110)	GA (N=110)	*P*-value
Incidence of nausea and vomiting, %	17	18	>0.005
Degree of pain control satisfaction	2.1±0.7	3.9±1.1	<0.005
Diclofenac dose (mg)	129.2±1.4	254±4.3	<0.005
Length of hospital stay (in days)	4.5±1.1	6.5±1.2	<0.005

Values expressed as mean ± SD for numerical variable. P value is based on Un paired t-test

The % of viable CD3+, CD4+, CD8+ and CD4+/CD8 ratio before and after treatment is presented in Figure 3. Results showed % of viable CD3+, CD4+, CD8+ and CD4+/CD8 ratio were marginally increased in patients treated with RA as compared to GA. As indicated in figure 3, the patients of both the treatment groups had greater reduction in T lymphocyte after treatment. However, reduction in T lymphocyte was significantly greater in patients

who received RA when compared to patients who received GA.

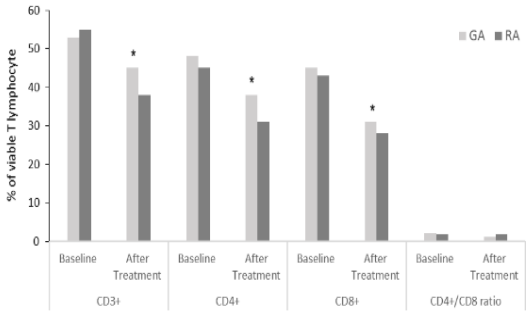

Figure 3: Comparison of RA and GA in terms T lymphocyte subcategories before and after treatment. * p<0.05 compared to reference, otherwise difference was not statistically significant (using unpaired test)

Overall, the level of inflammatory biomarkers such as IL-1, and hs CRP was significantly lesser in patients receiving RA as compared to those patients who received GA (Figure 4). As indicated in figure 4, patients of both treatment groups had greater reduction in T lymphocyte after treatment. However, reduction in T lymphocyte was significantly greater in patients who received RA when compared to patients who received GA.

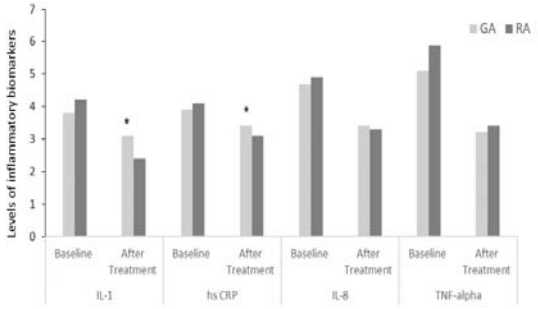

Figure 4: Comparison of RA and GA in terms inflammatory biomarkers before and after treatment. *P < 0.05 compared to reference, otherwise difference was not statistically significant (using unpaired test)

As indicated in Figure 5, patients of both treatment groups had similar memory score at baseline. However, improvement in memory score was greater in patients who received RA group when compared to patients who received GA. This indicates that the RA group demonstrates greater improvement in cognitive functions when compared to GA. As indicated in Figure 4, patients of both treatment groups had improvement in memory score after treatment.

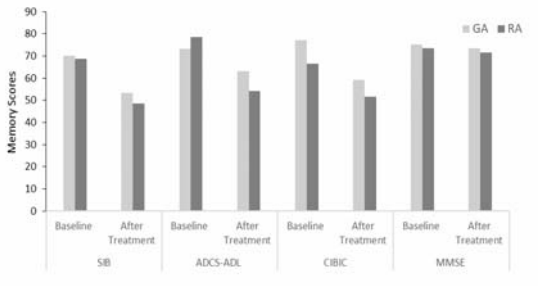

Figure 5: Comparison of RA and GA in terms of cognitive functions before and after treatment. Difference was not statistically significant (using unpaired test)

Survival outcome in both the treatment group were found to be comparable in both groups irrespective of the type of anesthesia used during the surgical intervention of metastatic cancer. This indicates that the use of anesthesia does not have any effect on survival outcome of metastatic cancer patient. Overall, incidence of nausea and vomiting was found comparable in both the groups. Post-operative results showed that the patients of both groups had comparable post-operative complications. The most common post-operative complications in patients of both groups were nausea/vomiting and CVS related complications followed by neurological related complication which were mild in severity. There was no statistically significant difference between both groups with regard to post-operative complications.

DISCUSSION

Surgery serves an important role in the management of metastatic cancer. However, 20 to 30% of subjects with advanced stage of cancer develop relapse in spite of surgical removal of cancerous cell. Approximately 15 % of cancer patients with early stage of gastric cancer had cure rate of more than 80 %. It was reported that surgical intervention causes surgical stress response and immunosuppression, which negatively impact the efficacy of anti-cancer drugs and causes severe impact on survival outcome and increase mortality cases among patients with metastatic cancer. A study reported that increased level of inflammatory biomarkers such as cytokines increases immunosuppressive properties, that result in tumor relapse and metastasis, that substantially reduced the survival period of cancer patients. Thus, controlling inflammatory reactions and protecting immune function during perioperative period is essential to achieve targeted therapeutic response in cancer patients [1-7].

In China, there is no study evaluating the effect of RA versus general anesthesia (GA) on postoperative opioid consumption, inflammatory biomarkers, cognitive function in Chinese patients undergoing metastatic cancer surgery. Hence, the present study was designed to compare the postoperative opioid consumption, inflammatory biomarkers, cognitive function and safety profile of RA versus GA in Chinese patients undergoing metastatic cancer surgery.

This study results showed that the levels of inflammatory biomarkers such as IL-1, hs CRP, TNF-alpha, and IL-8 were significantly less in patients received combination of RA as compared to those patients who received GA. This indicates that combination of RA inhibits inflammatory response by decreasing IL-1, hs CRP, TNF-alpha, and IL-8. Also, treatment with RA improved the level of T lymphocytes such as CD3+, CD4+, and CD8+. This result is consistent with previous reports that combination of RA inhibited inflammatory response as compared to patients that received GA, which indicates that RA improves immune response in patients undergoing surgical intervention [11-19]. It has been reported that increased level of inflammatory biomarkers such as cytokines increases immunosuppressive properties, that result in tumor relapse and metastasis, that substantially reduced the survival period of cancer patients. Thus, controlling inflammatory reactions and protecting immune function during perioperative period are necessary to achieve targeted therapeutic response in cancer patients.

This study results report that patients of both treatment groups had greater reduction in post-operative pain score at each time points. However, reduction in VAS score was significantly greater in patients who received RA as compared to patients who received GA. At the early timepoints, pain score after was significantly lower in patients who received RA as compared to GA. This indicates that the RA demonstrates significantly greater reduction in postoperative pain as compared to general anesthesia. This was further confirmed by postoperative opioid consumption, which was significantly lower in patient who received combination of RA as compared to GA from day 1 to 4.

The result of the present study is consistent with the previous reports that RA demonstrates significantly greater pain relief as compared to patients that received GA, which indicates that RA improves pain relief and improves recovery among patients undergoing surgical intervention [17,20,21]. During surgical intervention, several pain management options are available such as patient-controlled analgesia (PCA), regional analgesia and regional anesthesia including epidural that are more commonly used to manage post-operative pain. Opioid analgesics as PCA such as morphine and other derivatives are most frequently used for primary treatment as analgesia in patients undergoing major surgical intervention such as cancer surgery. However, the use of Opioids as PCA are commonly associated with adverse events such as sedation, nausea/vomiting, and pruritus.

In our study, survival outcome in both the treatment groups was comparable in both the irrespective of the type of anesthesia used during surgical intervention. The result of present study is consistent with the previous reports that RA demonstrates no clinical benefit in survival outcome as compared to patients that received GA, which indicates that RA has no role in improving survival outcome among patients undergoing surgical intervention [22]. The use of RA in cancer surgery is increasing nowadays due to its effect on metastasis/relapse of tumor postoperatively. Also, RA is likely to reduce the incidence of side effects and metastasis/relapse of tumor. Also, general anesthesia (GA) is commonly used in gastric cancer surgical innervations. The choice of anesthesia is vital in surgical intervention while performing surgical resection of tumor as it affects recovery, side effects and metastasis/relapse of tumor. Several studies reported interesting findings on the role of anesthetic techniques in improving prognosis of GC and reducing post-operative complications in GC patients undergoing surgical resection of the tumor. However, few studies reported that there was no relationship of anesthetic techniques and clinical prognosis of tumor.

Zhong *et al* [15] reported that the combination of RA and GA (RA plus GA) could improve the prognosis of tumor post-surgical interventions of ovarian cancer. Christopherson and his co-workers [16] showed that there are no long-term benefits of overall survival and disease-free survival outcome after surgical interventions of colon cancer using RA and GA. This study reports are consistent with the finding of Christopherson and his co-workers.

Limitations of the study

Since the present trial was conducted at a single hospital in China, the findings of the present trial cannot be generalized to the Chinese population. Due to lower sample size, the power of trial was less, thus, a large clinical trial with appropriate

sample size is needed to validate the present findings.

CONCLUSION

RA + GA demonstrates significantly greater improvement in the level of clinical outcomes, decreases postoperative opioid consumption and improves the cognitive functions when compared to GA in Chinese patients undergoing metastatic cancer surgery.

DECLARATIONS

Acknowledgement

Authors would like to thank patients and study staff for their support in conducting this study.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

The authors declare that this work was done by them and all liabilities pertaining to claims relating to the content of this article will be borne by them. Chunmei Xu and Fang Wang contributed to this work equally.

REFERENCES

1. *Desborough JP. The stress response to trauma and surgery, Br J Anaesth 2000; 85: 109-117.*
2. *Gottschalk A, Sharma S, Ford J, Durieux M, Tiouririne M. The Role of the Perioperative Period in Recurrence After Cancer Surgery. Anesth Analg 2010; 110: 1636-1643.*
3. *Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, Naritake Y, Hosokawa T, Kajiwara T. Suppression of Cellular Immunity by Surgical Stress. Surgery 2000; 127: 329-336.*
4. *Armaiz-Pena GN, Lutgendorf S, Cole S, Sood AK. Neuroendocrine modulation of cancer progression. Brain Behav Immun 2009; 23(1):10-15.*
5. *Langley RR, Fidler, IJ. Tumor Cell-Organ Microenvironment Interactions in the Pathogenesis of Cancer Metastasis. Endocr Rev 2007; 28:297-321.*
6. *Cheng YC, Cheng XB, Li XJ, Wang FZ,Li ZK. Combined general and regional anesthesia and effects on immune function in patients with benign ovarian tumors treated by laparoscopic therapy. Int J Clin Exp Med 2013; 6: 716-719.*
7. *Lingzhi W, Hailin Z, Hao W, Daqing M. Lasting effects of general anesthetics on the brain in the young and elderly: "mixed picture" of neurotoxicity, neuroprotection and cognitive impairment. J Anesth. 2019; 33(2): 321–335.*
8. *Wada H, Seki S, Takahashi T. Combined spinal and general anesthesia attenuates liver metastasis by preserving TH1/TH2 cytokine balance. Anaesthesiol 2007; 106: 499–506.9. Greisen J, Hokland M, Grofte T. Acute pain induces an instant increase in natural killer cell cytotoxicity in humans and this response is abolished by local anaesthesia. Br J Anaesth 1999; 83: 235–240.*
9. *Biki B, Mascha E, Moriarty DC. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: A retrospective analysis. Anaesthesiol 2008; 109: 180–187.*
10. *Hiller JG, Hacking MB, Link EK. Perioperative epidural analgesia reduces cancer recurrence after gastro-oesophageal surgery. Acta Anaesthesiol Scand 2014; 58: 281–290.*
11. *Cummings KC, Patel M, Htoo PT. A Comparison of the effects of epidural analgesia versus traditional pain management on outcomes after gastric cancer resection. Reg Anesth Pain Med 2014; 39: 200–207.*
12. *Gottschalk A, Ford JG, Regelin CC. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anaesthesiology 2010; 113: 27–34.*
13. *Cummings KC, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: A population-based study. Anesthesiology 2012; 116: 797–806.*
14. *Zhong S, Zhong X, Xiaomei Z, Liu Y. Comparison between the effect of epidural anesthesia combined with epidural analgesia and general anesthesia combined with intravenous analgesia on prognosis of ovarian cancer patients. Oncology letters 2019; 17(6):5662-5668.*
15. *Christopherson R, James KE, Tableman M. Long-term survival after colon cancer surgery: A variation associated with choice of anesthesia. Anesth Analg 2008; 107(1): 325–332.*
16. *Bao-Jun H, Ying D, Shu-Xin G, Jie F, Ran W, Hong D, Dan-Xia G, Li W, Yan-Ying W. General anesthesia combined with epidural anesthesia maintaining*

appropriate anesthesia depth may protect excessive production of inflammatory cytokines and stress hormones in colon cancer patients during and after surgery. Medicine (Baltimore) 2019;98(30): e16610.

17. *Yang Y. Effect of general anesthesia combined with epidural anesthesia on stress response, inflammatory reaction and coagulation in patients with colon Cancer. Journal of Hainan Medical University 2018; 24(18): 59-63.*
18. *Weigang L, Lixia W, Miao Z, Liming Z. Effects of general anesthesia with combined epidural anesthesia on inflammatory response in patients with early-stage gastric cancer undergoing tumor resection. Exp Ther Med 2019; 17(1): 35–40*
19. *Qin L. Effects of epidural combined with general anesthesia versus general anesthesia on quality of recovery of elderly patients undergoing laparoscopic radical resection of colorectal cancer: A prospective randomized trial. J Clin Anesth 2020; 62:109742.*
20. *Nan Li, Hao K, Shuang-Ling L, Sai-Nan Z, Dong-Xin W. Combined epidural-general anesthesia was associated with lower risk of postoperative complications in patients undergoing open abdominal surgery for pheochromocytoma: A retrospective cohort study. PLoS One 2018;13(2): e0192924.*
21. *Jiangling W, Wenjing G, Qicheng W, Runze Z, Jun F. Impact of Combination Epidural and General Anesthesia on the Long-Term Survival of Gastric Cancer Patients: A Retrospective Study. Med Sci Monit 2016; 22: 2379–2385.*