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Impact of Combination Epidural and General Anesthesia on the Long-Term Survival of Gastric Cancer Patients: A Retrospective Study

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Background: Whether regional anesthesia is associated with tumor-free and long-term survival is controversial. Here, we focused on whether epidural anesthesia affects the long-term survival of gastric cancer patients after surgery.

Material/Methods: We obtained the records of 273 patients undergoing gastric cancer surgery between August 2006 and December 2010. All patients received elective surgery, and the end-point was death. The general anesthesia group comprised 116 patients and the epidural-supplemented group comprised 157 patients. The results were analyzed using a multivariable model to determine the relationship between epidural use and long-term survival.

Results: No obvious association was detected between epidural use and long-term survival according to the Cox model ($P=0.522$); the adjusted estimated hazard ratio was 0.919 (95% CI 0.71–1.19). However, according to Kaplan-Meier analysis, epidural anesthesia was associated with long-term survival among younger patients (age up to 64) ($p=0.042$, log-rank) (but not among older patients ($p=0.203$, log-rank)). A lower American Society of Anesthesiologists (ASA) class and less chemoradiotherapy exposure were also associated with a longer survival. However, advanced tumor stage still has a significant negative impact on survival.

Conclusions: No obvious difference was detected between the 2 anesthesia groups, but younger patients may benefit from epidural anesthesia.

MeSH Keywords: **Anesthesia, Caudal • Stomach Neoplasms • Survivors**

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Background

Surgery is the first choice for the treatment of most solid tumors without metastasis. However, surgery releases tumor cells into the circulation [1]. Many studies have demonstrated that surgery can promote cancer metastasis by suppressing immunity and natural killer (NK) cell activity, both *in vivo* and *in vitro* [2,3]. Morphine- or fentanyl-based general anesthesia elicits an immunosuppressive effect by decreasing NK cell activity [4]. A stress response is an unavoidable adverse effect of general anesthesia [5,6]. Epidural anesthesia decreases the stress response after surgery, which can promote tumor metastasis [7–9]. Administration of opioids and inhaled anesthetics also contributes to increased NK cell activation during neural blockade. Studies have shown that epidural-supplemented anesthesia reduces cancer recurrence and postoperative mortality [8,9]. However, other studies found no association between anesthesia (epidural and non-epidural experimental groups) and survival or the recurrence of cancer after cancer surgery [10,11]. In another study, epidural anesthesia was associated with a lower recurrence of cancer after cancer surgery in patients older than 64 years. In a large cohort study, epidural anesthesia was associated with prolonged survival in cancer patients without metastasis; however, recurrence in these patients was unaffected [12]. Therefore, due to the conflicting results, we retrospectively analyzed 273 patients who underwent gastric cancer surgery. The endpoint was death. We sought to determine whether epidural-supplemented anesthesia is associated with prolonged survival.

Material and Methods

After we received approval from the Review Board and Ethics Committee of Zhejiang Cancer Hospital, we collected the clinical records of 273 patients who underwent primary gastric cancer resection between August 2006 and December 2010. The follow-up ended at death, and the longest follow-up period lasted nearly 8 years (September 2006 to September 2014). In total, 116 patients were in the non-epidural group, and 157 patients were in the epidural-supplemented group.

Epidural anesthesia was administered in gastric cancer patients except for those with low blood volume, shock, local infection/surgery/trauma/malformation, bacteremia that may cause epidural infection, low coagulation status or insufficient stopping time anticoagulant, children, mental illness, and patients who refused the epidural.

General anesthesia was induced with 0.5 µg/Kg sufentanil (Yichang Humanwell Pharmaceutical Co. Ltd. Yichang, Hubei, China) 1.3–3.0 mg/Kg propofol (AstraZeneca, UK), and 30–50 µg/Kg midazolam in patients of both groups. Anesthesia

was maintained with 4–12 mg/Kg propofol and 0.5–1.0 µg/Kg remifentanyl in the non-epidural group. Remifentanyl (Yichang Humanwell Pharmaceutical Co. Ltd. Yichang, Hubei, China) was replaced with 0.25% levobupivacaine (Rundu, Zhuhai, China) or ropivacaine (AstraZeneca, UK) via an epidural catheter in the epidural group.

We identified factors that may influence survival after surgery. These factors included age, sex, ASA class, tumor stage, anesthetic technique, surgical method, hemorrhage volume during the operation, and radiotherapy with or without chemotherapy, as well as a history of hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease, liver disease, or any other disease. The TNM (topography, lymph node, and metastasis) staging was also obtained, and the tumors were divided into stages 0–IV based on the pathologic staging system that was in use when the surgery was originally performed.

The data were recorded in Excel, and SPSS statistical analysis software was the main tool used for data analyses. Normally distributed continuous variables were compared using independent-samples *t* tests. Non-normally distributed variables were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square or Fisher's exact tests. We used the Kaplan-Meier log-rank test for univariate analyses and the Cox proportional hazards regression model for multivariate analyses of the survival time after cancer surgery.

All factors that affect survival time after cancer surgery were selected as the main effects in the multivariate Cox model. The significance level for each hypothesis was 0.05. We used SPSS Statistics version 22.0.0.0 (IBM Corp. USA).

Results

All baseline factors, including perioperative and postoperative risk factors, were compared between the groups (Table 1). There were more men in the epidural group.

The median survival times for cancer patients were 13.15 (7.1–21.95) and 13.2 (7.8–23.0) months for patients in the non-epidural and epidural-supplemented groups, respectively. No difference was found between the groups ($p=0.541$).

The Kaplan-Meier analysis indicated no association between epidural-supplemented anesthesia and prolonged survival ($p=0.680$ log-rank), as shown in Figure 1. However, epidural anesthesia increased the long-term survival in patients younger than 65 years ($p=0.035$ log-rank test) (Figure 2).

The multivariate Cox regression model indicated no significant association between epidural use and prolonged survival after

Table 1. Patient characteristics in two types of anesthesia techniques.

Factor	Level	Non Epidural (N=116)		Epidural (N=157)		P Value
Baseline						
Age Yr.		70	(63, 78)	67	(59, 76)	0.033
Sex	Male	86	(74)	115	(73)	0.869*
ASA	I	52	(45)	82	(52)	0.432*
	II	50	(43)	58	(37)	
	III	13	(11)	17	(11)	
	IV	1	(0)	0	(0)	
ST**	1	92	(79)	119	(76)	0.536*
	2	18	(16)	32	(20)	
	3	6	(5)	6	(4)	
Stage***	I	5	(4)	6	(4)	0.599*
	II	1	(0)	10	(6)	
	III	42	(36)	67	(43)	
	IV	68	(59)	74	(47)	
T****	T1	2	(2)	3	(2)	0.601*
	T2	8	(7)	9	(6)	
	T3	27	(23)	48	(31)	
	T4	79	(68)	97	(62)	
N*****	N0	9	(8)	15	(10)	0.627*
	N1	10	(9)	15	(10)	
	N2	14	(12)	26	(17)	
	N3	83	(72)	101	(64)	
M*****	M0	13	(11)	10	(6)	0.155*
	M1	103	(89)	147	(94)	
EBL (ml)		300	(212, 400)	300	(200, 400)	0.337
RC	Yes	53	(46)	72	(46)	0.978*
HBP	Yes	18	(16)	15	(10)	0.135*
DIA	Yes	4	(3)	5	(3)	0.904*
CHD	Yes	3	(3)	2	(1)	0.424*
HEP	Yes	15	(13)	18	(11)	0.713*
COPD	Yes	2	(2)	3	(2)	0.909*
OTH	Yes	30	(26)	47	(30)	0.46*

Statistics are median (Q1, Q3), or N (%), as appropriate. Wilcoxon Rank Sum Test unless specified. * Pearson chi-square test.
 *** Tumor stage, stage 0 – Tis; N0, M0; stage I – T1, N0, M0/T2, N0, M0; stage II – T1 N1 M0/T2 N1 M0/T3, N0, M0/T1, N3, M0/T3 N1 M0/T2 N2 M0/T4a N0 M0; stage III – T2–4a, N3, M0/T3–4b, N2, M0/T4 N0–1 M0; stage IV – any T, any N, M1. **** T0, no evidence of primary tumor; T1, invasion *via* submucosa into lamina; T2, invasion into the muscularis propria; T3, invasion through the subserosa; T4, invasion of surrounding structures. ***** N0, no lymph nodes involved; N1, one to two nodes involved; N2, three or seven nodes involved. N3, seven or more nodes involved. ***** M0, no metastasis; M1, metastasis. ** Surgical Technique, 1, Distal gastrectomy with Billroth I or Billroth II reconstruction; 2, Total gastrectomy with Roux-en-Y Gastric Bypass surgery. 3, Other surgical techniques not specified. CHD – coronary heart disease; HEP – hepatopathy; COPD – chronic obstructive pulmonary disease; OTH – other disease not specified. ASA – American Society of Anesthesiologists; ST – surgical technique; T – topograph; N – lymph node; M – metastasis; EBL – estimated blood loss; RC – radiotherapy and/or chemotherapy; HBP – hypertension; DIA – diabetes; OTH – other disease not specified.

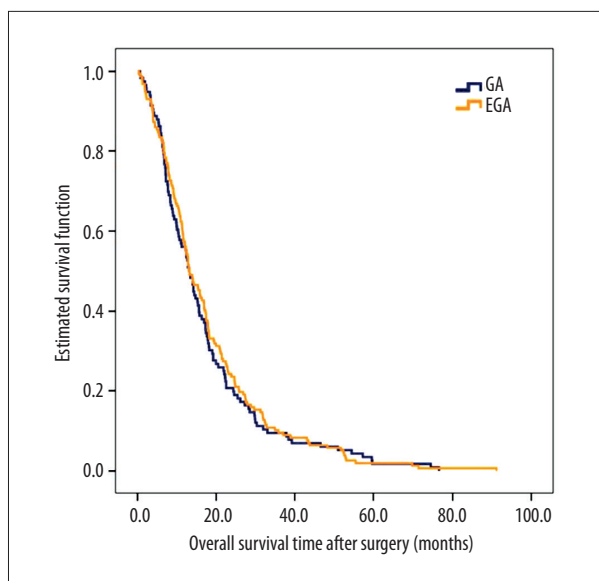


Figure 1. Kaplan-Meier time to overall survival curve for epidural and non-epidural groups. Log-rank test, $P=0.68$. GA represents general anesthesia, EGA represents general anesthesia-based epidural anesthesia.

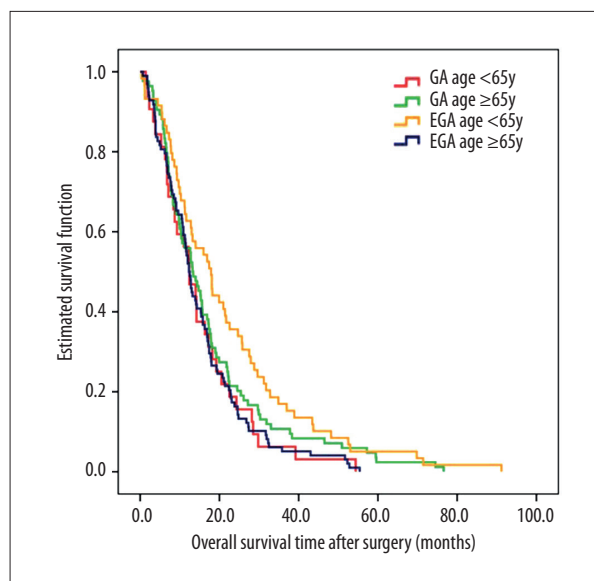


Figure 2. Epidural use and age categories, Kaplan-Meier curves for overall survival time in epidural and non-epidural groups by age categories. Log-rank test, $P=0.035$. GA represents general anesthesia, EGA represents general anesthesia-based epidural anesthesia.

cancer surgery ($p=0.522$), and the adjusted estimated hazard ratio was 0.919 (95% CI 0.71–1.19) (Table 2). Table 3 shows the main effects for another multivariate Cox model. ASA status, tumor clinical stage, and chemoradiotherapy still affect prolonged survival after gastric cancer surgery.

Discussion

Currently, whether epidural anesthesia prolongs the survival of cancer patients after surgery is controversial. Biki [8], and Hiller [9] demonstrated that epidural use is associated with lengthened survival in patients receiving surgery for prostatic carcinoma, pancreatic adenocarcinoma, and gastro-esophageal cancer. In contrast, studies by Christopherson [13] and Myles [14] showed no association between epidural anesthesia and prolonged survival in patients receiving surgery for gastric, colorectal, gastro-esophageal, non-small cell lung, and abdominal cancers. A Cochrane Review addressing this topic showed no survival benefit for the 2 groups by using a fixed-effects model with an HR of 1.03 (95% CI 0.86–1.24) in the pooled results [15].

In recent decades, scientists have focused on the effects of perioperative factors and interventions on cancer recurrence and overall survival. Many factors are involved in cancer recurrence and overall survival, including tumor type, tumor stage and size, surgical skill and techniques, anesthetic technique, radiotherapy with or without chemotherapy, blood loss, and transfusions

during the perioperative period. Other factors include comorbid diseases, such as hypertension, immunodeficiency, diabetes, or chronic obstructive pulmonary disease. The mixed results of the present study are difficult to interpret. Further investigation is needed before a reliable conclusion can be drawn.

The stress of surgery negatively affects the adaptive immune system [16]. Because immune surveillance is the first indicator for preventing cancer metastasis, immune suppression or disturbance may decrease the defensive barrier against intruders such as tumor cells, as well as inflammation. Immune suppression may then facilitate cancer cell migration and lead to cancer recurrence at either a local or distant site. The suppression of NK cell activity due to the stress of surgery promotes tumor movement [17–20]. Some anesthetics such as opioids and inhaled anesthetics may inhibit immune function, including NK cell activity, lymphocyte proliferative responses to mitogens, and phagocytic activity [8,18,19]. Morphine and fentanyl have been well studied for their ability to suppress NK cell cytotoxicity [4].

Local anesthesia is traditionally used for surgery. As previously described, the limited use of opioids during local anesthesia may attenuate the suppression of NK cell cytotoxicity. Studies also support this hypothesis [9–12]. Additionally, regional anesthesia inhibits the surgical stress response and is linked to earlier recovery times by reducing the incidence of thromboembolic, pulmonary, and gastrointestinal complications, as well as inflammation after major surgery [20,21].

Table 2. COX regression results for multivariable of baseline factors.

Baseline factors	P value	Hazard ratio	95.0% CI	
Sex	.336	.863	.639	1.165
Age	.386	.994	.979	1.008
Anesthetic technique	.522	.919	.710	1.190
ASA Status (I)	.002		*	
ASA Status (II)	.472	.471	.061	3.662
ASA Status (III)	.914	.894	.118	6.775
ASA Status (IV)	.867	.839	.108	6.549
Stage (I) **	.000	.494	.373	.653
Stage (II)	.022	.437	.216	.886
Stage (III)	.001	.321	.166	.621
Stage (IV)	.000	.494	.373	.653
Surgical technique 1***	.836		*	
Surgical technique 2	.954	1.018	.557	1.861
Surgical technique 3	.712	1.134	.582	2.207
Radiotherapy and/or chemotherapy	.000	1.968	1.472	2.630
Estimate blood loss	.809	1.000	.999	1.001
Transfusion	.508	1.000	.999	1.001
Hypertension	.419	1.199	.772	1.862
Diabetes	.072	2.166	.933	5.029
Chronic heart disease	.532	.725	.264	1.988
Hepatopathy	.704	1.086	.710	1.660
Chronic obstructive pulmonary disease	.830	.890	.306	2.588
Other disease	.695	1.061	.790	1.423

Estimated overall survival function of each factor in multivariable COX regression model. * No Estimated of hazard ratio (95% confidence interval [CI]) provided because of very large proportion (96%) of "yes." ** Tumor stage, stage 0 – Tis; N0, M0; stage I – T1, N0, M0/T2, N0, M0; stage II – T1 N1 M0/T2 N1 M0/T3, N0, M0/T1, N3, M0/T3 N1 M0/T2 N2 M0/T4a N0 M0; stage III – T2–4a, N3, M0/T3–4b, N2, M0/T4 N0–1 M0; stage IV – any T, any N, M1. *** Surgical technique, 1, Distal gastrectomy with Billroth I or Billroth II reconstruction; 2, Total gastrectomy with Roux-en-Y Gastric Bypass surgery. 3, Other surgical techniques not specified.

The conclusion of this study is consistent with that reached by Cakmakaya [15] that epidural anesthesia is not associated with the overall survival of gastric cancer patients after surgery. However, there were some differences between this study and previous studies. Hiller [9] found that effective epidural analgesia improved the estimated median time to death among participants who received surgery for gastro-esophageal cancer. This study focused on gastric cancer patients who underwent surgery at the same hospital, and the study end-point

was death. Interestingly, we found that epidurals improved the long-term survival of younger patients (aged 65 years or younger). Because of the complex effects involved, we still have not reached a conclusion concerning the direct interaction between epidural use and prolonged survival after gastric cancer surgery. The beneficial effect observed in younger patients may be attributed to their education level, better health, and better immunity, or the administration of postoperative chemotherapy with or without radiotherapy.

Table 3. COX multivariable regression results

Factors	P value	Hazard ratio	95.0% CI	
			Low	Up
Age	.961	1.000	.987	1.013
Anesthetic technique	.422	.901	.699	1.161
ASA Status (I)	.005			
ASA Status (II)	.564	.557	.076	4.062
ASA Status (III)	.946	.933	.129	6.778
ASA Status (IV)	.741	.712	.095	5.325
Stage (I) *	.000			
Stage (II)	.032	.490	.255	.941
Stage (III)	.001	.347	.184	.655
Stage (IV)	.000	.522	.401	.679
Radiotherapy and/or chemotherapy	.000	1.873	1.424	2.464

for main effectors. Estimated overall survival function of main factors in multivariable COX regression model. * Tumor stage, stage 0 – Tis; N0, M0; stage I – T1, N0, M0/T2, N0, M0; stage II – T1 N1 M0/T2 N1 M0/T3, N0, M0/T1, N3, M0/T3 N1 M0/T2 N2 M0/T4a N0 M0; stage III – T2–4a, N3, M0/T3–4b, N2, M0/T4 N0–1 M0; stage IV – any T, any N, M1.

The majority of gastric cancer surgeries were performed in less than 2 hours in our hospital. Fluid infusion during the surgery was continuous with a crystal: colloid ratio of 2: 1 during a period of 2 hours. The surgical and anesthesia techniques were performed according to standard procedures. The outcomes for cancer patients can be influenced by many factors (described above).

The present study has certain limitations. Retrospective studies have inherent weaknesses, including susceptibility to bias, selection bias, and confounding variables. Moreover, the classification of gastric cancer has been changed, so “misclassification” in the past may have biased and nullified the result today. Also, the non-epidural group may have received other analgesics, which would increase the heterogeneity of the group.

This retrospective study was unable to demonstrate any significant benefit for survival after the administration of epidural anesthesia during gastric cancer surgery. More results from randomized controlled trials, such as studies sponsored

by The Cleveland Clinic [22], are needed to draw a reliable conclusion. Our group is preparing a randomized controlled study on this topic.

Conclusions

According to the results of the Mann-Whitney U test, the median survival after surgery for patients receiving epidural anesthesia was 17.1 months (range, 10.0–52.8 months). Epidural anesthesia combined with general anesthesia during gastric cancer surgery had no effect on the long-term survival according to the Cox proportional hazards regression model. Younger patients who received epidurals were more likely to have longer survival after surgery.

Conflicts of interest

The authors declare no financial support or conflict of interest.

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