Supplement 2

For: Ya-Ting Du, Ya-Wei Li, Bin-Jiang Zhao, et al. Long-term survival after combined epidural-general anesthesia or general anesthesia alone: Follow-up of a randomized trial.

Contents

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A

Recurrence-Free Survival (%)

General anesthesia alone

Combined epidural-general anesthesia

Adjusted hazard ratio 0.97, 95% CI 0.84 to 1.12; *P* = 0.692

Time after Surgery (month)
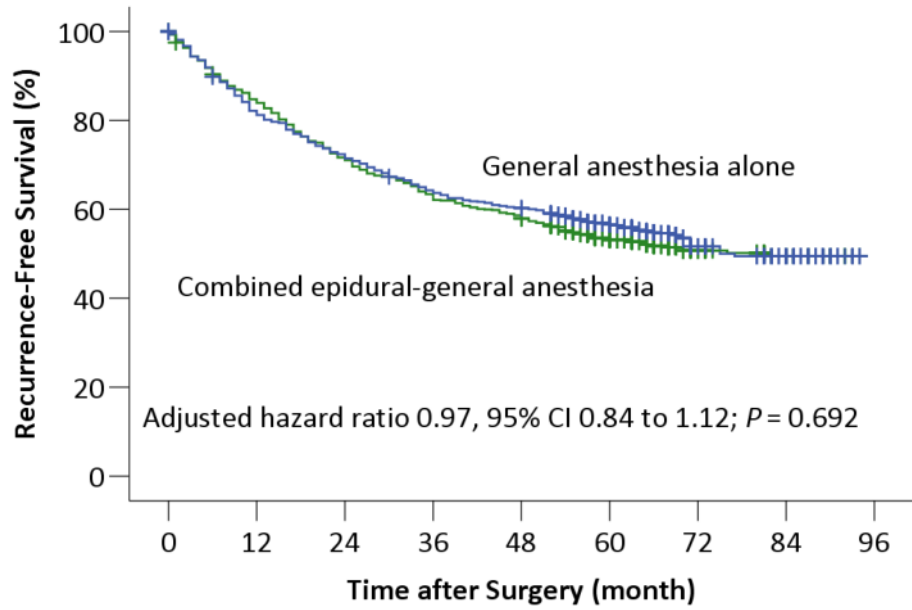
Number at risk

Combined epidural-general	853	704	596	521	486	332	133	72	72
General anesthesia	859	691	608	541	512	362	136	89	89

B

Event-Free Survival (%)

General anesthesia alone

Combined epidural-general anesthesia

Adjusted hazard ratio 0.99, 95% CI 0.86 to 1.12; *P* = 0.815

Time after Surgery (month)
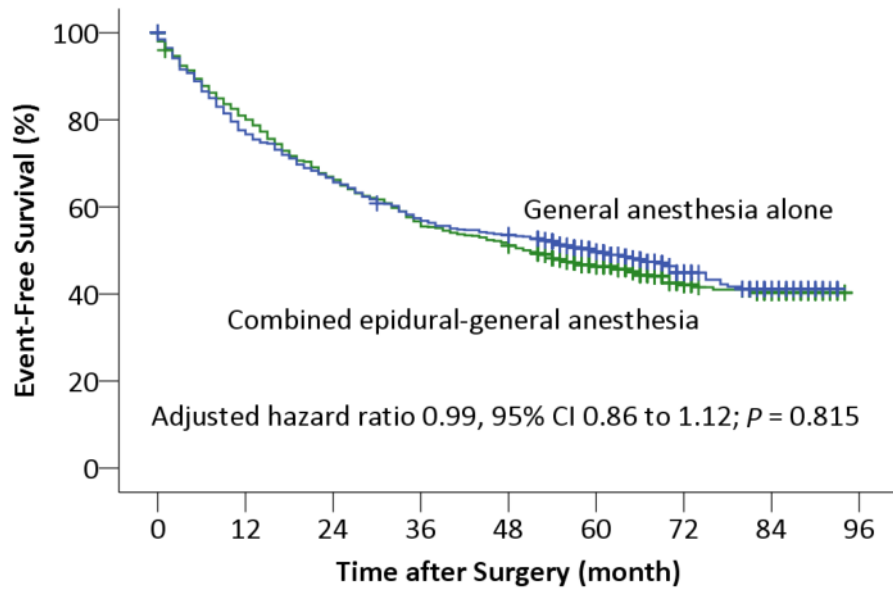
Number at risk

Combined epidural-general	853	672	556	466	429	293	92	57	57
General anesthesia	859	653	559	483	455	314	118	77	77

Figure S1. The Kaplan–Meier survival curves of all patients.

The Kaplan–Meier survival curves for (A) recurrence-free survival and (B) event-free survival. Multivariable Cox proportional hazards model adjusted for age, sex, body mass index, Charlson Comorbidity Index, type of surgery, location of surgery, type of cancer, Tumor-Node-Metastasis stage, and study center. Crosses indicate censored patients.

A

Overall Survival (%)

General anesthesia alone

Combined epidural-general anesthesia

Adjusted hazard ratio 1.06, 95% CI 0.91 to 1.24; $P = 0.449$

Time after Surgery (month)
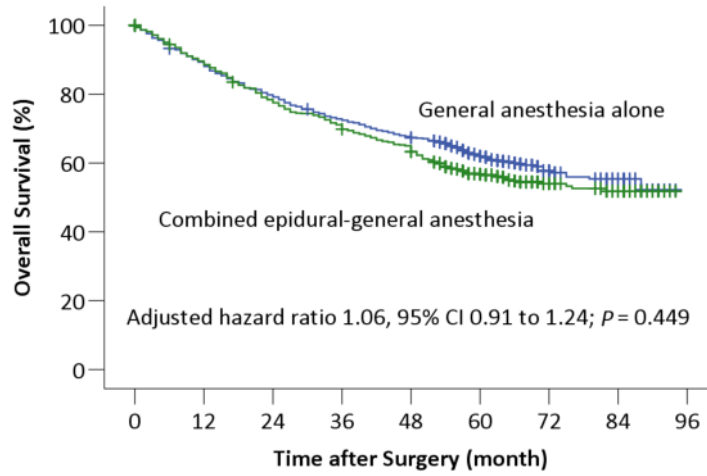
Number at risk

	0	12	24	36	48	60	72	84	96
Combined epidural-general	781	681	595	536	485	320	106	61	61
General anesthesia	793	693	623	569	529	365	133	91	33

B

Cancer-Specific Survival (%)

General anesthesia alone

Combined epidural-general anesthesia

Adjusted hazard ratio 1.09, 95% CI 0.93 to 1.28; $P = 0.290$

Time after Surgery (month)

Number at risk

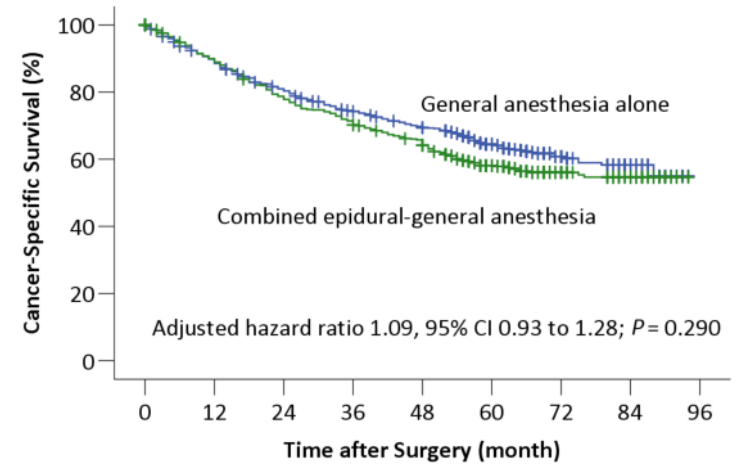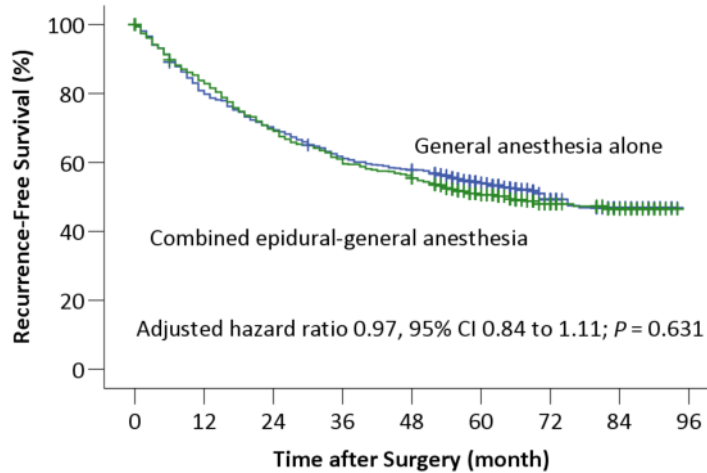|	0	12	24	36	48	60	72	84	96
Combined epidural-general	781	681	595	537	486	356	174	77	77
General anesthesia	793	693	623	570	529	386	134	91	33

C

Recurrence-Free Survival (%)

General anesthesia alone

Combined epidural-general anesthesia

Adjusted hazard ratio 0.97, 95% CI 0.84 to 1.11; $P = 0.631$

Time after Surgery (month)

Number at risk

	0	12	24	36	48	60	72	84	96
Combined epidural-general	781	637	531	458	426	287	111	58	58
General anesthesia	793	628	546	480	454	317	116	77	77

D

Event-Free Survival (%)

General anesthesia alone

Combined epidural-general anesthesia

Adjusted hazard ratio 0.98, 95% CI 0.86 to 1.12; $P = 0.743$

Time after Surgery (month)
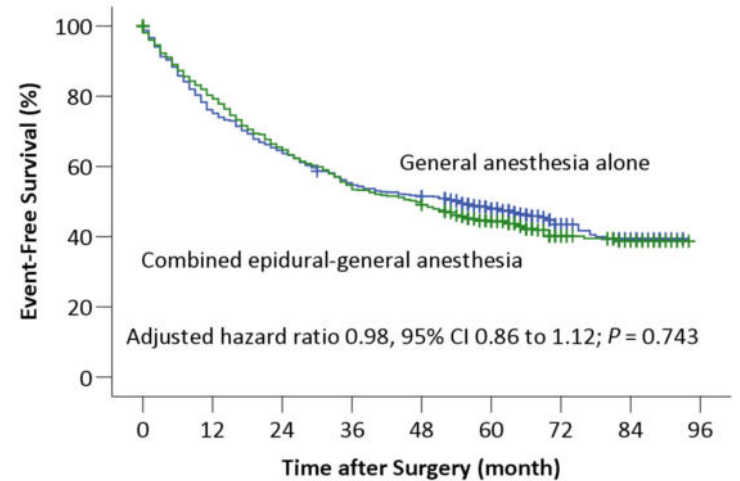
Number at risk

	0	12	24	36	48	60	72	84	96
Combined epidural-general	781	610	498	411	378	256	94	47	47
General anesthesia	793	592	502	430	405	277	102	67	67

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Figure S2. The Kaplan–Meier survival curves of cancer patients.

The Kaplan–Meier survival curves of (A) overall survival; (B) cancer-specific survival; (C) recurrence-free survival; and, (D) event-free survival in cancer patients. Multivariable Cox proportional hazards model adjusted for age, sex, body mass index, Charlson Comorbidity Index, type of surgery, location of surgery, type of cancer, Tumor-Node-Metastasis stage, and study center. Crosses indicate censored patients.

	Combined epidural-general anesthesia	General anesthesia alone	Hazard ratio for overall survival (95% CI)	Interaction P value
	Events/total (n/N)			
Age				0.144
<70 years	179/422	146/410	1.16 (0.93, 1.45)	
≥70 years	163/359	170/383	0.94 (0.76, 1.17)	
Sex				0.867
Male	231/509	220/540	1.05 (0.87, 1.27)	
Female	111/272	96/253	1.08 (0.82, 1.42)	
Body mass index				0.915
≤24 kg/m²	197/431	184/435	0.98 (0.80, 1.20)	
>24 kg/m²	145/350	132/358	1.19 (0.4, 1.51)	
Charslon Comorbidity Index				0.886
≤2	213/501	184/503	1.13 (0.93,1.38)	
>2	129/280	132/290	0.95 (0.74,1.22)	
Type of surgery				0.300
Mini-invasive	54/251	65/272	0.83 (0.57, 1.21)	
Open	288/530	251/521	1.10 (0.93, 1.31)	
Location of surgery				0.527
Intra-thoracic	80/180	71/171	1.22 (0.88, 1.70)	
Intra-abdominal	262/601	245/622	1.03 (0.86, 1.23)	
Type of cancer				0.283
Gastrointestinal	107/292	103/295	0.90 (0.68, 1.19)	
Hepatobiliary-pancreatic	62/80	55/71	1.01 (0.69, 1.47)	
Lung-esophageal-thymic	80/180	71/171	1.22 (0.88, 1.70)	
Other cancers	93/229	87/256	1.10 (0.82, 1.49)	
TNM stage				0.983
≤I	38/184	49/196	0.89 (0.58, 1.36)	
II	101/249	94/282	1.27 (0.95, 1.69)	
≥III	203/348	173/315	1.03 (0.84, 1.26)	
Study center				0.429
Center 1	313/714	286/726	1.08 (0.92, 1.27)	
Other centers	29/67	30/67	0.70 (0.40, 1.24)	

0.5 1.0 1.5 2.0

← Favors combined anesthesia   Favors general anesthesia →
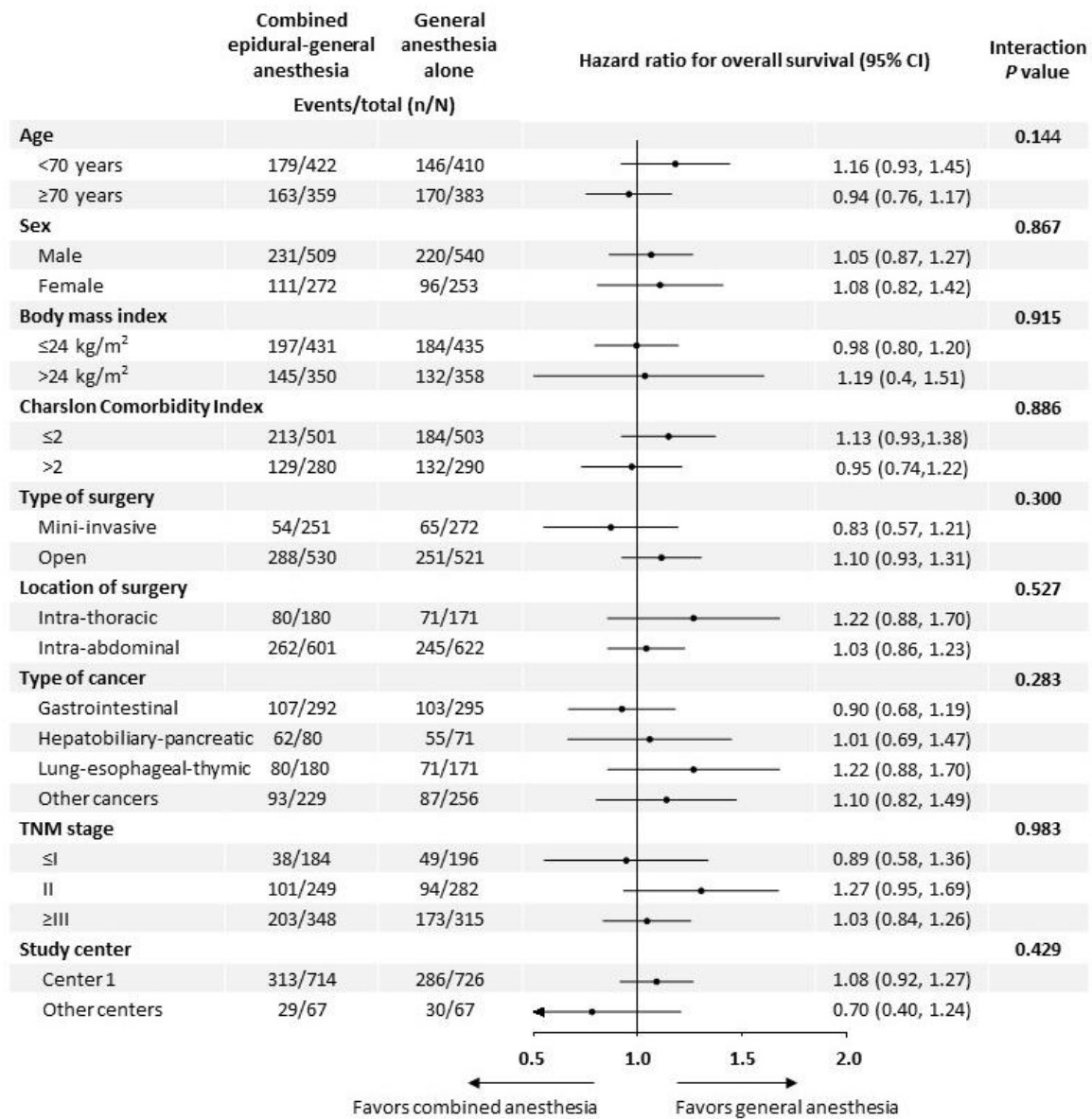
Figure S3. Forest plot in cancer patients.

Forest plot assessing interactions between preselected baseline factors and the effect of combined epidural-general anesthesia versus general anesthesia alone on overall survival in cancer patients. Hazard ratios and adjusted 95% CIs are shown. The estimated overall hazard ratio was derived from a multivariable Cox proportional hazards model adjusted for preselected baseline factors of age, sex, body mass index, Charlson Comorbidity Index, type of surgery, location of surgery, type of cancer, Tumor-Node-Metastasis stage, and study center. For the subgroup analyses, we assessed the treatment-by-covariate interaction on the primary outcome, adjusting for the same baseline variables.

Table S1. Baseline data of cancer patients

	Combined epidural-general anesthesia (n=781)	General anesthesia alone (n=793)	ASD
Age, year	69±6	70±6	0.070
Male sex, n (%)	509 (65)	540 (68)	0.062
Body mass index, kg/m^2	24±3	24±3	0.027
Education, year	10 ± 5	10 ± 4	0.001
Comorbidity, n (%)			
Stroke	33 (4)	42 (5)	0.050
Transient ischemic attack	9 (1)	12 (2)	0.031
Hypertension	305 (39)	348 (44)	0.098
Coronary heart disease	79 (10)	70 (9)	0.044
Arrhythmia	25 (3)	33 (4)	0.051
Chronic bronchitis	17 (2)	12 (2)	0.049
COPD	14 (2)	15 (2)	0.007
Asthma	14 (2)	13 (2)	0.012
Diabetes	138 (18)	146 (18)	0.019
Thyroid disease [a]	21 (3)	18 (2)	0.027
Liver dysfunction [b]	6 (<1)	4 (<1)	0.033
Renal dysfunction [c]	4 (<1)	3 (<1)	0.020
Previous cancer [d]	14 (2)	15 (2)	0.007
Chronic smoking, n (%) [e]	193 (25)	193 (24)	0.009
Alcoholism, n (%) [f]	59 (8)	55 (7)	0.024
Charlson Comorbidity Index [g]	2 (2-3)	2 (2-3)	0.044
History of anesthesia, n (%)	357 (46)	368 (46)	0.014
NYHA classification, n (%)			0.006
Class I	588 (75)	599 (76)	
Class II	193 (25)	194 (24)	
ASA classification, n (%)			0.054
Class I	60 (8)	56 (7)	
Class II	672 (86)	676 (85)	
Class III	49 (6)	61 (8)	
Preoperative laboratory test results			
Hematocrit, %	38.0 ± 5.2	38.1 ± 5.4	0.019
Albumin, g/L	40.1 ± 4.3	40.1 ± 4.4 [1]	<0.001
Glucose <4.0 or >10.0 mmol/L, n (%)	42 (5)	53 (7)	0.055
Na$^+$<135.0 or >145.0 mmol/L, n (%)	43 (6)	64 (8)	0.102
K$^+$<3.5 or >5.5 mmol/L, n (%)	77 (10)	73 (9)	0.022
Creatinine >133 μmol/L, n (%)	17 (2)	27 (3)	0.075
Preoperative delirium, n (%)	0 (<1)	0 (<1)	<0.001
Mini-Mental State Examination, score [h]	29 (27, 30) [10]	29 (27, 30) [11]	0.039
Barthel index, score [i]	100 (100, 100) [10]	100 (100, 100) [8]	0.039
Pathologically diagnosed cancer, n (%)	781 (100)	793 (100)	<0.001
Study centers, n (%)			0.021
Center 1	714 (91)	726 (92)	
Center 2	17 (2)	12 (2)	
Center 3	17 (2)	16 (2)	

Center 5	1 (<1)	3 (<1)	
Center 6	32 (4)	36 (5)	

Data are mean ± SD, n (%) or median (IQR). Numbers in square brackets indicate patients with missing data.

Abbreviations: ASD, absolute standardized difference (an ASD of ≥0.095 is considered imbalanced between the two groups); COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; ASA, American Society of Anesthesiologists.

[a] Included hyperthyroidism, hypothyroidism, nodular goitre, Hashimoto's thyroiditis and thyroid adenoma.

[b] Alanine transaminase and/or aspartate transaminase higher than 5 times the upper normal limit.

[c] Creatinine >177 μmol/L.

[d] Confirmed by pathological examination.

[e] Smoking half a pack (10 cigarettes) per day for at least 1 year, either former or current smoker.

[f] Two drinks or more daily, or weekly consumption of the equivalent of 150 mL of alcohol.

[g] According to the Charlson Comorbidity Index without age.

[h] Score ranges from 0 to 30, with higher score indicating better function.

[i] Score ranges from 0 to 100, with higher score indicating better function.

Table S2. Type and pathological stage of cancer patients

	Combined epidural-general anesthesia (n=781)	General anesthesia alone (n=793)	ASD
Type of cancer, n (%)			0.044
Gastric	76 (10) [a]	89 (11) [b]	
Small intestine	8 (1)	6 (<1)	
Appendix	0 (<1)	1 (<1)	
Colorectal	208 (27) [c]	199 (25) [d]	
Liver	39 (5)	28 (4)	
Biliary duct	12 (2)	16 (2)	
Gallbladder	5 (<1)	9 (1)	
Pancreatic	24 (3)	18 (2)	
Lung	146 (19)	125 (16)	
Esophageal	31 (4)	43 (5)	
Malignant thymoma	3 (<1)	3 (<1)	
Renal	48 (6)	45 (6)	
Urinary bladder	83 (11)	90 (11)	
Ureter	23 (3)	32 (4)	
Prostate	58 (7)	78 (10)	
Pelvic cavity	17 (2) [e]	11 (1) [f]	
Tumor-Node-Metastasis stage [g]			
Tumor stage, n (%)			0.043
Tx	0 (<1)	0 (<1)	
T_0	0 (<1)	0 (<1)	
Ta	8 (1)	4 (<1)	
Tis	5 (<1)	7 (<1)	
T_1	145 (19)	169 (21)	
T_2	221 (28)	216 (27)	
T_3	288 (37)	292 (37)	
T_4	114 (15)	105 (13)	
Node stage, n (%)			0.117
Nx	6 (<1)	3 (<1)	
N_0	508 (65)	560 (71)	
N_1	138 (18)	124 (16)	
N_2	108 (14)	89 (11)	
N_3	21 (3)	17 (2)	
Metastasis stage, n (%)			0.082
Mx	1 (<1)	1 (<1)	
M_0	696 (89)	725 (91)	
M_1	84 (11)	67 (8)	

Data are n (%).

Abbreviations: ASD, absolute standardized difference (an ASD of ≥.095 is considered imbalanced between the two groups).

[a] Include gastric cancer (68 cases) and malignant gastric stromal tumor (8 cases).

[b] Include gastric cancer (79 cases) and malignant gastric stromal tumor (10 cases).

[c] Include colon cancer (113 cases), and rectal cancer (95 cases).

[d] Include colon cancer (98 cases), and rectal cancer (101 cases).

[e] Include cervical cancer (1 case), ovarian cancer (4 cases), malignant tumor of the vulva and vagina (1 case), liposarcoma (6 cases), leiomyosarcoma (1 case), malignant peripheral nerve sheath tumor (1 case), and malignant fibrous histiocytoma (3 cases).

[f] Include cervical cancer (2 cases), ovarian cancer (2 cases), liposarcoma (5 cases), malignant peripheral nerve sheath tumors (2 cases).

[g] According to the American Joint Committee on Cancer 8th Edition Cancer Staging System.

Table S3. Perioperative and follow-up data of cancer patients

	Combined epidural-general anesthesia (n=781)	General anesthesia alone (n=793)	*P* value
Intraoperative data			
Duration of anesthesia, h	4.9 (3.8, 6.1)	4.9 (3.8, 6.2)	0.820
Intraoperative medications			
Midazolam, mg	1.5 (1.0, 2.0)	1.5 (1.2, 2.0)	0.376
Propofol, mg	780 (220, 1195)	840 (290, 1280)	0.106
Use of nitrous oxide, n (%)	492 (63)	560 (71)	0.001
Use of sevoflurane, n (%)	399 (51)	456 (58)	0.011
Remifentanil, μg	140 (0, 800)	1200 (600, 1880)	<0.001
Sufentanil, μg	20 (15, 30)	35 (25, 45)	<0.001
Use of vasopressors, n (%) [a]	451 (58)	356 (45)	<0.001
Use of glucocorticoids, n (%) [b]	711 (91)	716 (90)	0.611
Intraoperative MAP, mmHg [c]	79±7	83±7	<0.001
SBP <80 mmHg, min	0 (0, 4)	0 (0, 2)	<0.001
SBP >180 mmHg, min	0 (0, 0)	0 (0, 2)	<0.001
Intraoperative HR, bpm [c]	69±10	67±10	0.005
HR <40 bpm, min	0 (0, 0)	0 (0, 0)	0.736
HR >100 bpm, min	0 (0, 2)	0 (0, 2)	0.206
Duration of surgery, h	3.9 (2.8, 5.1)	3.9 (2.9, 5.2)	0.941
Location of surgery, n (%)			0.480
Intra-thoracic	180 (23)	171 (22)	
Intra-abdominal	601 (77)	622 (78)	
Type of surgery, n (%)			0.363
Open	530 (68)	521 (66)	
Thoraco-/laparoscopic	251 (32)	272 (34)	
Estimated blood loss, mL	100 (50, 300)	150 (50, 350)	0.568
Intraoperative blood transfusion, n (%)	115 (15)	133 (17)	0.265
Postoperative data			
ICU admission after surgery, n (%)	151 (19)	166 (21)	0.429
With endotracheal intubation, n (%)	71 (9)	102 (13)	0.017
Postoperative opioid analgesia			
Epidural sufentanil, μg	124 (118, 125)	0 (0, 0)	<0.001
Intravenous morphine, mg	0 (0, 0)	43 (38, 50)	<0.001
Supplemental opioids, n (%)	90 (12)	88 (11)	0.789
Delirium within 7 days, n (%)	13 (2)	41 (5)	<0.001
Other complications within 30 days, n (%)	174 (22)	197 (25)	0.231
Length of hospital stay, d	9 (7, 13)	9 (7, 13)	0.461
30-day mortality, n (%)	6 (<1)	2 (<1)	0.278
Perioperative data			
Sufentanil equivalent, ug [d]	165 (145, 225)	204 (148, 275)	<0.001
Use of NSAIDs, n (%) [e]	339 (43)	378 (48)	0.090
Long-term follow-up data			
Time to last follow-up, month [f]	66 (60, 80)	66 (61, 80	0.883
Postoperative anti-cancer therapy, n (%)	266 (35) [12]	243 (31) [5]	0.114
Radiotherapy	30 (4) [12]	45 (6) [5]	0.095

Chemotherapy	203 (26) [12]	178 (23) [5]	0.080
Reoperation	41 (5) [12]	32 (4) [5]	0.236
Interventional therapy	8 (1) [12]	13 (2) [5]	0.411

Data are median (IQR), n (%), or mean ± SD. Numbers in square brackets indicate patients with missing data.

Abbreviations: MAP, mean arterial pressure; SBP, systolic blood pressure; HR, heart rate; bpm, beats per minute; ICU, intensive care unit; NSAIDs, non-steroid anti-inflammatory drugs.

[a] Include ephedrine, phenylephrine, vasopressin, epinephrine, and norepinephrine.

[b] Include dexamethasone, methylprednisolone and hydrocortisone.

[c] Average value during anesthesia.

[d] Include those administered intra- and postoperatively (up to 7 days after surgery). Sufentanil 10 μg (iv) = sufentanil 10 μg (epidural) = fentanyl 100 μg (iv) = remifentanil 100 μg (iv) = morphine 10 mg (iv) = morphine 30 mg (po) = oxycodone 15 mg (po)= dezocine 10 mg (iv) = tramadol 100 mg (iv) = pethidine 100 mg (iv).

[e] Include flurbiprofen axetil and parecoxib administered intra- and postoperatively, up to 7 days after surgery.

[f] From the date of surgery to September 30, 2019.

Table S4. Individual new onset cancer and new serious non-cancer diseases during follow-up

	All patients			Cancer patients		
	Combined epidural-general anesthesia (n=853)	General anesthesia alone (n=859)	*P* value	Combined epidural-general anesthesia (n=781)	General anesthesia alone (n=793)	*P* value
New onset cancer. [a]			0.884			0.875
Lung	2	2		1	1	
Thyroid	2	1		2	1	
Colon	3	2		3	1	
Bladder	2	4		2	4	
Pelvis and ureter	1	1		1	1	
Porta hepatis bile duct	1	0		0	0	
Lymphoma	1	0		0	0	
Oropharynx	0	1		0	1	
Epityphlon	0	1		0	1	
Kidney	0	2		0	1	
Prostate	0	1		0	1	
Leg	1	0		1	0	
New serious non-cancer disease. [b]			0.233			0.140
Stroke	8	11		5	8	
Valvular heart disease	2	0		2	0	
Acute myocardial infarction	3	8		3	8	
Arrhythmia	3	3		1	2	
Stent implantation	3	1		2	0	
Thrombus	5	2		5	2	
Atelectasis	3	3		3	3	
Pulmonary embolism	1	1		1	1	
Pulmonary nodules	2	1		2	1	
Intestinal obstruction	18	15		17	14	
Gall-stone	2	2		1	1	
Urethrostenosis	1	1		1	1	
Tracheostenosis	1	1		1	1	

Esophageal stenosis	0	2		0	2	
Infection	8	14		5	12	
Fractures	4	8		4	8	
Prostatic hyperplasia	4	1		3	1	
Cataract	3	4		3	4	
Polyps	5	7		5	7	
Benign tumor	2	3		2	3	
Hernia	5	10		5	9	
Glaucoma	1	1		0	1	
Fistula	2	2		2	2	
Cirrhosis	0	2		0	2	
Intestinal rupture	1	0		1	0	
Gastric ulcer with hemorrhage	0	1		0	1	

Data are number.

[a] Indicate those that were pathologically confirmed and differing from the primary tumor.

[b] Indicate those that required hospital readmission and/or another surgery.

Table S5. Cognitive function and quality of life in 3-year survivors

	Combined epidural-general anesthesia (n=853)	General anesthesia alone (n=859)	Estimated mean difference (95% CI) [a]	*P* value
TICS-m , score	33.6±5.2 (n=581)	33.3±4.9 (n=609)	0.4 (-0.2, 0.9)	0.209
WHOQOL-BREF, score	(n=587)	(n=614)		
Physical domain	63.4±14.6	61.5±12.2	1.9 (0.4, 3.4)	0.015
Psychological domain	60.5±13.7	58.9±12.1	1.6 (0.1, 3.1)	0.033
Social relationships domain	57.8±13.6	56.9±12.5	0.8 (-0.6, 2.3)	0.262
Environment domain	59.5±12.9	58.8±12.4	0.7 (-0.8, 2.1)	0.369

Data are mean ± SD.

Abbreviations: TICS-m, the Telephone Interview for Cognitive Status-modified; WHOQOL-BREF, the World Health Organization Quality of Life-Brief version.

[a] Calculated as the combined epidural-general anesthesia group vs. or minus the general anesthesia group.