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Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in limb-salvage surgery for osteosarcoma

A retrospective analysis

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Abstract

Previous studies have demonstrated that anesthetic techniques can affect the outcomes of cancer surgery. We investigated the association between anesthetic techniques and patient outcomes after elective limb-salvage surgery for osteosarcoma (OS). This was a retrospective cohort study of patients who underwent elective limb-salvage surgery for OS between January 2007 and December 2018. Patients were grouped according to the administration of propofol-based total intravenous anesthesia (TIVA) or desflurane (DES) anesthesia. Kaplan–Meier analysis was performed, and survival curves were constructed from the date of surgery to death. Univariate and multivariate Cox regression models were applied to compare the hazard ratios (HRs) for death after propensity matching. Subgroup analyses were done for postoperative recurrence, metastasis, and tumor–node–metastasis (TNM) staging. A total of 30 patients (17 deaths, 56.7%) who received DES anesthesia and 26 (4 deaths, 15.4%) who received TIVA were eligible for analysis. After propensity matching, 22 patients were included in each group. In the matched analysis, patients who received TIVA had better survival with a HR of 0.30 (95% confidence interval [CI], 0.11–0.81; $P = .018$). Subgroup analyses also showed significantly better survival in the presence of postoperative metastasis (HR, 0.24; 95% CI, 0.06–0.87; $P = .030$) and with TNM stage II to III (HR, 0.26; 95% CI, 0.09–0.73; $P = .011$) in the matched TIVA group. In addition, patients administered with TIVA had lower risks of postoperative recurrence and metastasis than those administered with DES anesthesia in the matched analyses. Propofol-based TIVA was associated with better survival in patients who underwent elective limb-salvage surgery for OS than DES anesthesia. Prospective studies are needed to assess the effects of TIVA on oncological outcomes in patients with OS.

Abbreviations: ALP = alkaline phosphatase, ASA = American Society of Anesthesiologists, CCI = Charlson comorbidity index, CI = confidence interval, DES = desflurane, HR = hazard ratio, INHA = inhalation anesthetic, LDH = lactic dehydrogenase, MET = metabolic equivalent, OS = osteosarcoma, PS = propensity score, TIVA = total intravenous anesthesia, TNM = tumor–node–metastasis, TSGH = Tri-Service General Hospital, VA = volatile anesthesia.

Keywords: cancer surgery, desflurane, osteosarcoma, propofol, survival

1. Introduction

Osteosarcoma (OS) is the most common primary bone cancer in children and young adults and typically has a bimodal distribution pattern with incidence peaks in the second decade of life and in late adulthood (>60 years old).[1–3] The incidence rates of OS in the bimodal age groups are 4.4 and 4.2 per million, respectively.[1,3] Although OS develops

ZFW and WCT contributed equally to this work.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was approved by the ethical committee of Tri-Service General Hospital (TSGHIRB No: B202105037).

All data analyzed during this study are included in the article.

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rarely, it is characterized by a high degree of malignancy, strong invasiveness, rapid disease progression, and a high mortality rate. The 5-year survival rate of OS in children and adolescents is 61.6%, but it drops drastically to 24.2% in elderly individuals.[3] Limb-salvage surgery has been the mainstay of therapy for OS and is conducted with the aim of achieving complete resection of the disease and preserving limb function.[1,2] However, surgical stress may impair immune responses and upregulate adhesion molecules through mechanisms involving ischemia-reperfusion injury, activation of sympathetic nervous system, inflammation, and systemically hypercoagulable state.[4] Potential tumor cell dissemination and immunosuppression collectively produce a microenvironment favorable for the development of cancer recurrence and metastasis. Accordingly, there is increasing interest in the impact of perioperative settings on cancer progression.

Evidence reveals that different anesthetic techniques can affect immune function and tumor progression in various pathways.[4–6] Experimental studies have shown that inhalation anesthetics (INHAs) may alter immunological processes and subsequently increase metastatic potential,[7–9] whereas propofol maintains the integrity of immunity and reduces the tendency towards cancer recurrence or metastasis.[9–11] The effects of volatile anesthesia (VA) and propofol-based total intravenous anesthesia (TIVA) have also been reported in clinical settings, indicating the superiority of TIVA over VA in cancer surgery.[12–15] Moreover, there are retrospective studies suggesting that TIVA produces better long-term outcomes than VA post-surgery in different types of cancers.[16–25] However, some studies show that anesthetics do not have definite effects on cancer immunity and patient outcomes.[26–30] Notably, a meta-analysis shows that TIVA is generally associated with better overall survival than VA in cancer surgery, especially in patients administered with desflurane (DES) anesthesia.[31]

To the best of our knowledge, no study has compared the effects of propofol and INHAs on patient outcomes after OS surgery. We hypothesized that TIVA was associated with greater overall survival than DES anesthesia, as in our previous studies.[18–25] As a result, we conducted a retrospective analysis to assess the relationship between the type of anesthesia and cancer outcomes after limb-salvage surgery for OS and to identify potential risk factors for mortality.

2. Materials and Methods

2.1. Study design and setting

This retrospective cohort study was conducted at Tri-Service General Hospital (TSGH), Taipei, Taiwan.

2.2. Participants and data sources

The ethics committee of TSGH approved this retrospective study and waived the need for informed consent (TSGHIRB No: B202105037). We retrieved relevant information from medical records and electronic database at TSGH for 56 patients with an American Society of Anesthesiologists (ASA) score of II to III who had undergone elective limb-salvage surgery for tumor–node–metastasis (TNM) stage I to III OS between January 2007 and December 2018. Patients included in the study were treated with either propofol-based TIVA (n = 26) or DES anesthesia (n = 30), based on the anesthesiologist's preference.

The exclusion criteria were TIVA combined with INHAs or regional analgesia, amputation surgery, metastatic bone tumor, non-OS histology, and incomplete data. Ultimately, 135 patients were excluded from this analysis (Fig. 1).

2.3. Anesthetic techniques

The anesthetic techniques were applied as previously reported.[18–25,29] In brief, general anesthesia (GA) was maintained with propofol at an effect-site concentration (Ce) of 3.0 to 4.0 mcg/mL using a target-controlled infusion (TCI) system in the TIVA group. On the other hand, in the DES group, the DES vaporizer was set between 4% and 10%. Based on patients' hemodynamics, the maintenance of GA with DES and the Ce of propofol using a TCI pump were adjusted upward and downward by 0.5 to 2% and 0.2 to 0.5 mcg/mL, respectively. Repetitive bolus injections of opioids and neuromuscular blocking agents were given as required during surgery.

During maintenance of GA, all patients received a fraction of inspired oxygen of 100% oxygen at a flow rate of 300 mL/min in a closed breathing system. The level of end-tidal carbon dioxide was maintained at 35–45 mm Hg by adjusting the ventilation rate in the volume control model with a tidal volume of 6–8 mL/kg and a maximum airway pressure <30 cmH_2O. Postoperatively, all patients were extubated and transferred to the post-anesthesia care unit for postoperative observation and care.[18–22,24,25,29]

2.4. Variables

We retrospectively collected the following patient data: anesthetic technique, time since the earliest included patient serving as a surrogate of the calendar year, calendar period, sex, age at the time of surgery, habitus, cancer location and size, presence of pathologic fracture, TNM stage and histological grade, and serum levels of alkaline phosphatase (ALP) and lactic dehydrogenase (LDH). For serum ALP and LDH values, patients were grouped according to ALP values of >129 or ≤129 IU/L and LDH values of >271 or ≤271 IU/L, respectively, because elevated ALP and LDH levels were associated with poor survival in patients with OS.[32,33]

The Charlson comorbidity index (CCI) of 0 to 37 (least to highest comorbidity) was used to predict the 10-year survival in patients with multiple comorbidities. In addition, preoperative functional status was evaluated in metabolic equivalents (METs), and patients were grouped according to a functional status of ≥4 or <4 METs because those with a functional capacity of <4 METs during daily activities had increased perioperative cardiac and long-term risks.[34]

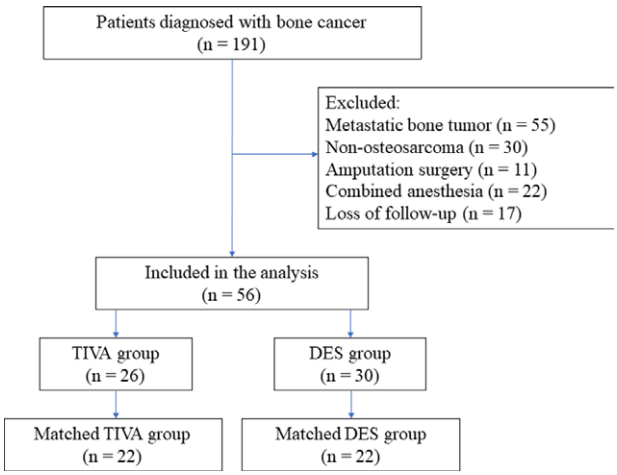

Figure 1. Flow diagram detailing the selection of patients included in the retrospective analysis. A total of 135 patients were excluded owing to combined propofol anesthesia with inhalation anesthetics or regional analgesia, metastatic bone tumor, non-osteosarcoma, incomplete data, or undergoing amputation surgery. DES = desflurane, TIVA = total intravenous anesthesia.

Other data included the ASA physical status score from I to V (lowest to highest morbidity), administration of neoadjuvant or adjuvant chemotherapy and adjuvant radiotherapy, need for intraoperative blood transfusion, use of postoperative nonsteroidal anti-inflammatory drugs (NSAIDs), operation and anesthesia time, grade of surgical complications scaled by the Clavien–Dindo classification from 0 (no complication) to V (death), hospital stay, presence of postoperative recurrence or metastasis, and mortality. Based on causes of death, patients who died at the follow-up period from the date of surgery to December 31, 2019 were recorded as all-cause or cancer-specific mortality. All-cause mortality was defined that patients died due to various causes including cancer-related or not; cancer-specific mortality was defined that patients died only from cancer-related causes. Because these variables had been known or posited to affect patient outcomes, they were chosen as potential confounders.

2.5. Statistical methods

The primary outcome was overall survival compared between the TIVA and DES groups. Survival time was defined as the interval between the date of surgery and the date of death or December 31, 2019, for patients who were censored. All data are presented as mean ± standard deviation (SD) or numbers (percentage).

Patient characteristics and mortality rates were compared between the groups administered with different anesthetics using Student *t* test or chi-squared test. Survival according to the anesthetic technique was depicted visually using a Kaplan–Meier survival curve. The relationship between the anesthetic technique (TIVA or DES anesthesia) and survival was analyzed using the Cox proportional hazards model with and without adjustment for variables noted previously. Overall survival from the date of surgery grouped according to the anesthetic technique and other variables was compared separately in a univariate Cox model and subsequently in a multivariate Cox regression model. Variables that were significant in the univariate model proceeded to perform the multivariate analysis, but postoperative recurrence and metastasis were excluded to avoid multicollinearity. We also conducted subgroup analyses for all-cause mortality, cancer-specific mortality, presence of postoperative recurrence or metastasis, different TNM stages, and disease progression between the two anesthetic techniques.

Propensity score (PS) matching using IBM SPSS Statistics (version 23.0; IBM SPSS Inc., Chicago, IL) was applied to select the most similar PSs for preoperative variables (with caliper sets at 0.2 SD of the logit of the PS) across each anesthesia: propofol or DES in a 1:1 ratio, ensuring the comparability between TIVA and DES anesthesia before surgery. Preoperative variables for performing PS matching included time since the earliest included patient, sex, age, body mass index (BMI), CCI, ASA class, cancer location and size, presence of pathologic fracture, TNM stage, preoperative serum levels of ALP and LDH, and administration of neoadjuvant chemotherapy. Because calendar period, functional status and histological grade were highly correlated with time since the earliest included patient, ASA class and TNM stage, respectively, these variables were excluded to increase the rigorousness of PS matching. Statistical significance was set at P value < 0.05.

3. Results

3.1. Patient and treatment characteristics

Patient and treatment characteristics are shown in Table 1. The time since the earliest included patient, calendar period, sex, age, BMI, CCI, ASA score, preoperative functional status, cancer location and size, presence of pathologic fracture, TNM stage and histological grade, serum ALP and LDH levels, administration of neoadjuvant or adjuvant chemotherapy and adjuvant radiotherapy, need for intraoperative blood transfusion, use of postoperative NSAIDs, operation and anesthesia time, grade of surgical complications, and hospital stay were not significantly different between the two anesthetic techniques (Table 1).

PS matching is a crucial statistical method to minimize the effect of confounding factors in observational studies.[35] Therefore, we used the PS from the logistic regression to adjust the baseline characteristics and the choice of treatment between the two anesthetic techniques. A total of 22 pairs were formed after matching. Patient characteristics and treatment factors of OS were not significantly different between the matched groups, except for the calendar period (Table 1).

A greater percentage of patients in the DES group (66.7%) had postoperative recurrence compared to the TIVA group (26.9%; P = .007). The incidence of postoperative metastasis was also significantly higher in the DES group (50.0%) than in the TIVA group (15.4%; P = .014). The all-cause mortality rate was significantly lower in the TIVA group (15.4%) than in the DES group (56.7%; P = .004) during follow-up. Furthermore, cancer-specific mortality equated to all-cause mortality in this study because all postoperative deaths resulted from cancer. Hence, the cancer-specific mortality rate was significantly lower in the TIVA group (15.4%) than in the DES group (56.7%; P = .004) during follow-up. After PS matching, the results were consistent between the two anesthetic techniques, except for postoperative metastasis (Table 1). The incidence of postoperative recurrence was significantly lower in the matched TIVA group (31.8%) than in the matched DES group (68.2%; P = .035); however, there was no significant difference in postoperative metastasis between the matched groups (P = .106). The all-cause and cancer-specific mortality rates were significantly lower in the matched TIVA group (18.2%) than in the matched DES group (54.5%; P = .028). The median follow-up period was 4.66 years for the TIVA group and 2.56 years for the DES group. Kaplan–Meier survival curves for the two anesthetic techniques are shown in Figure 2A and B. In addition, the cumulative incidence of cancer relapse is shown in Figure 3A and B.

3.2. Risks of overall mortality

The risk of overall mortality associated with the administration of TIVA and DES anesthesia during limb-salvage surgery for OS is shown in Table 2. Patients who received TIVA had better overall survival than those who received DES anesthesia (overall survival, 84.6% vs 43.3%, respectively; hazard ratio [HR], 0.20; 95% confidence interval [CI], 0.07–0.60; P = .004). In the multivariate model after adjustment for CCI, ASA score, serum ALP and LDH levels, TNM stage, administration of adjuvant chemotherapy and radiotherapy, and intraoperative blood transfusion, patients in the TIVA group were also associated with improved overall survival compared to those in the DES group (HR, 0.09; 95% CI, 0.02–0.36; P = .001). Another variable that significantly increased the mortality risk after the multivariate analysis was higher baseline ALP level (P = .004) (Table 2).

3.3. Subgroup analyses

The subgroup analyses for all-cause mortality, cancer-specific mortality, presence of postoperative recurrence and metastasis, TNM staging, and disease progression are shown in Table 3. There were no interaction effects between the type of anesthesia and postoperative recurrence (P = .941), postoperative metastasis (P = .950), and TNM stage (P = .950) on survival. All analyses were stratified according to the presence of postoperative recurrence and metastasis, and different TNM stages.

3.3.1. All-cause mortality and cancer-specific mortality. In the all-cause and cancer-specific mortality analysis, patients in

Table 1

Patient and treatment characteristics for overall group and matched group after propensity scoring.

Variables	Overall patients			Matched patients			
	TIVA (n = 26)	DES (n = 30)	*P* value	TIVA (n = 22)	DES (n = 22)	*P* value	SMD
Time since the earliest included patient (yr), mean (SD)	5.82 (3.14)	5.28 (3.23)	.527	5.84 (3.31)	4.01 (2.72)	.052	0.604
Calendar period, n (%)			.420			.023	0.658
2007–2010	8 (30.8)	10 (33.3)		7 (31.8)	10 (45.5)		
2011–2014	7 (26.9)	12 (40.0)		5 (22.7)	10 (45.5)		
2015–2018	11 (42.3)	8 (26.7)		10 (45.5)	2 (9.0)		
Sex (male),n (%)	17 (65.4)	16 (53.3)	.521	13 (59.1)	12 (54.5)	1.000	0.093
Age (yr old), n (%)			.623			.809	0.053
10–30	18 (69.2)	17 (56.7)		15 (68.2)	15 (68.2)		
31–59	2 (7.7)	3 (10.0)		1 (4.5)	2 (9.1)		
≧60	6 (23.1)	10 (33.3)		6 (27.3)	5 (22.7)		
BMI (kg/m^2), mean (SD)	23.95 (4.28)	23.49 (3.46)	.657	23.71 (4.30)	22.94 (3.32)	.511	0.200
Charlson comorbidity index,mean (SD)	2.88 (1.58)	3.33 (1.79)	.328	3.05 (1.68)	3.00 (1.69)	.929	0.030
ASA class, n (%)			.582			1.000	0.106
II	20 (76.9)	20 (66.7)		16 (72.7)	17 (77.3)		
III	6 (23.1)	10 (33.3)		6 (27.3)	5 (22.7)		
Functional status (≧4 METs), n (%)	20 (76.9)	20 (66.7)	.582	16 (72.7)	17 (77.3)	1.000	0.106
Tumor location, n (%)			.509			.099	0.146
Femur	10 (38.5)	13 (43.3)		8 (36.4)	10 (45.5)		
Tibia	9 (34.6)	11 (36.7)		8 (36.4)	9 (40.9)		
Humerus	6 (23.1)	3 (10.0)		5 (22.7)	0 (0.0)		
Fibula	1 (3.8)	3 (10.0)		1 (4.5)	3 (13.6)		
Tumor size (≧8 cm), n (%)	8 (30.8)	12 (40.0)	.660	6 (27.3)	10 (45.5)	.347	0.385
Pathologic fracture, n (%)	2 (7.7)	2 (6.7)	1.000	2 (9.1)	2 (9.1)	1.000	0.000
ALP (>129 IU/L), n (%)	5 (19.2)	10 (33.3)	.376	5 (22.7)	8 (36.4)	.509	0.303
LDH (>271 IU/L), n (%)	9 (34.6)	14 (46.7)	.521	8 (36.4)	10 (45.5)	.759	0.186
TNM stage of primary tumor, n (%)			.623			1.000	0.000
I	7 (26.9)	11 (36.7)		7 (31.8)	7 (31.8)		
II–III	19 (73.1)	19 (63.3)		15 (68.2)	15 (68.2)		
Histological grade of primary tumor, n (%)			.449			.931	0.054
I	7 (26.9)	11 (36.7)		7 (31.8)	7 (31.8)		
II	9 (34.6)	6 (20.0)		6 (27.3)	5 (22.7)		
III	10 (38.5)	13 (43.3)		9 (40.9)	10 (45.5)		
Neoadjuvant chemotherapy, n (%)	16 (61.5)	15 (50.0)	.551	12 (54.5)	13 (59.1)	1.000	0.093
Adjuvant chemotherapy, n (%)	17 (65.4)	17 (56.7)	.695	13 (59.1)	15 (68.2)	.754	NA
Adjuvant radiotherapy, n (%)	6 (23.1)	6 (20.0)	1.000	6 (27.3)	4 (18.2)	.719	NA
Intraoperative transfusion, n (%)	10 (38.5)	10 (33.3)	.905	9 (40.9)	9 (40.9)	1.000	NA
Postoperative NSAID, n (%)	14 (53.8)	16 (53.3)	1.000	11 (50.0)	15 (68.2)	.358	NA
Operation time (min),mean (SD)	212.04 (61.18)	219.07 (66.41)	.684	210.64 (60.24)	218.91 (73.98)	.686	NA
Anesthesia time (min),mean (SD)	237.31 (62.23)	243.87 (68.39)	.711	235.73 (61.44)	243.23 (76.01)	.721	NA
Grade of surgical complications, n (%)			.650			.907	NA
0	5 (19.2)	9 (30.0)		4 (18.2)	3 (13.6)		
I	11 (42.3)	11 (36.7)		9 (40.9)	10 (45.5)		
II	10 (38.5)	10 (33.3)		9 (40.9)	9 (40.9)		
Length ofhospitalstay (d), mean (SD)	13.19 (4.49)	12.77 (5.47)	.754	13.77 (4.63)	13.64 (5.37)	.929	NA
Postoperative recurrence, n (%)	7 (26.9)	20 (66.7)	.007	7 (31.8)	15 (68.2)	.035	NA
Postoperative metastasis, n (%)	4 (15.4)	15 (50.0)	.014	4 (18.2)	10 (45.5)	.106	NA
All-cause mortality, n (%)	4 (15.4)	17 (56.7)	.004	4 (18.2)	12 (54.5)	.028	NA
Cancer-specific mortality, n (%)	4 (15.4)	17 (56.7)	.004	4 (18.2)	12 (54.5)	.028	NA

Notes: Data shown as mean ± SD or n (%). Grade of surgical complications: Clavien–Dindo classification.

ALP = alkaline phosphatase, ASA = American Society of Anesthesiologists, BMI = body mass index, DES = desflurane, LDH = lactic dehydrogenase, MET = metabolic equivalent, NA = not applicable, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation, SMD = standardized mean difference, TIVA = total intravenous anesthesia, TNM = tumor–node–metastasis.

the TIVA group showed better survival than those in the DES group. The crude HR was 0.20 (95% CI, 0.07–0.60; $P = .004$), and the PS-matched HR was 0.30 (95% CI, 0.11–0.81; $P = .018$) (Table 3).

3.3.2. Postoperative recurrence. Regarding the presence of postoperative recurrence, patients who received TIVA did not show significantly better survival than those who received DES anesthesia. For patients with postoperative recurrence, the crude HR was 0.53 (95% CI, 0.21–1.38; $P = .197$), and the PS-matched HR was 0.65 (95% CI, 0.22–1.89; $P = .426$) (Table 3).

3.3.3. Postoperative metastasis. Patients with postoperative metastasis who received TIVA had better survival than those who received DES anesthesia. For patients with postoperative metastasis, the crude HR was 0.25 (95% CI, 0.08–0.78; $P = .017$), and the PS-matched HR was 0.24 (95% CI, 0.06–0.87; $P = .030$). Accordingly, patients who received TIVA had lower metastasis-specific mortality than those who received DES anesthesia (Table 3).

3.3.4. TNM stage. Patients with TNM stage II to III who received TIVA had better survival than those who received DES anesthesia. For patients with TNM stage II to III, the crude HR was 0.17 (95% CI, 0.07–0.44; $P < .001$), and the PS-matched HR was 0.26 (95% CI, 0.09–0.73; $P = .011$) (Table 3). Therefore, TIVA was associated with better outcomes in OS patients with late TNM stage (II–III) than DES anesthesia.

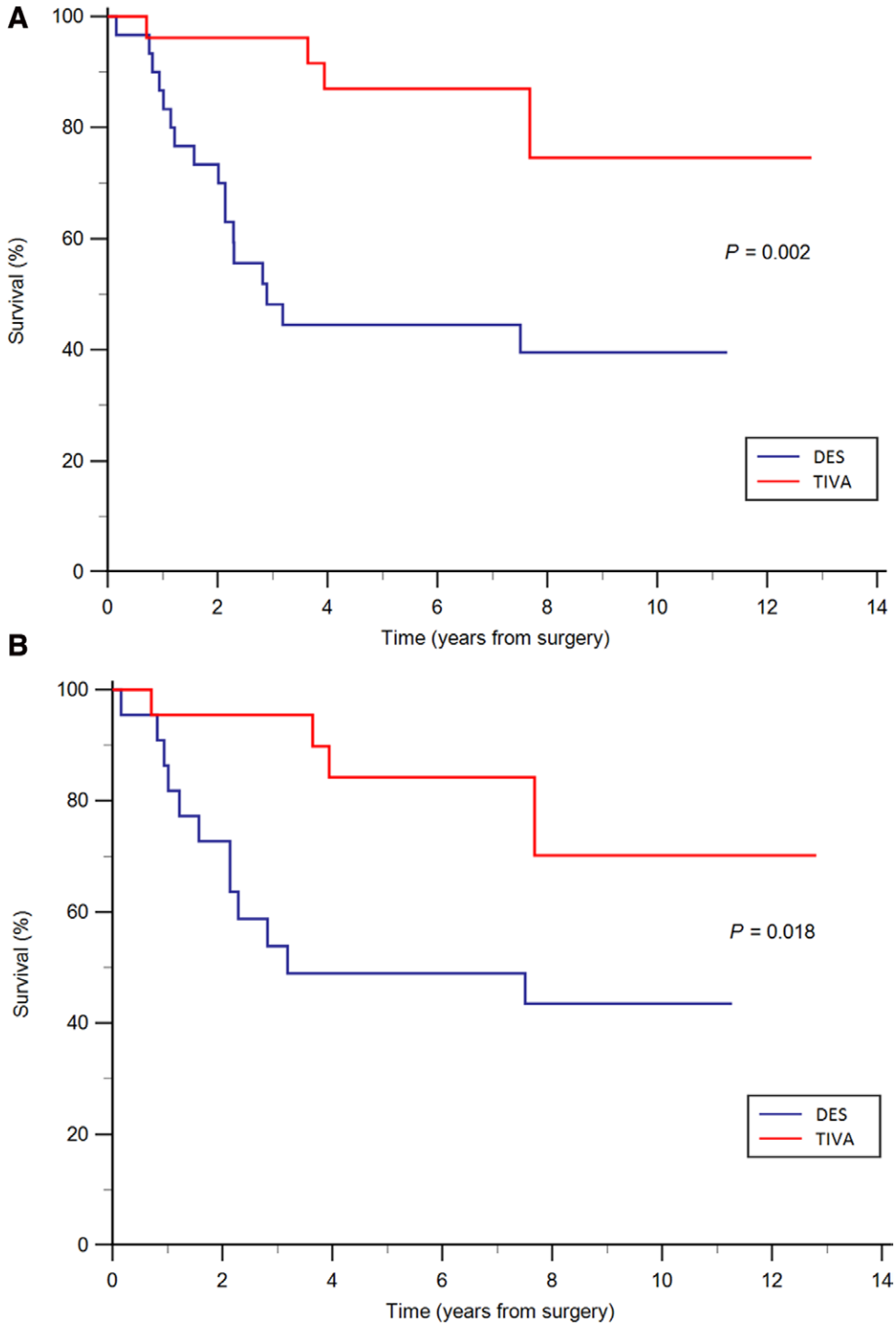

Figure 2. (A) Overall survival curves from the date of surgery by anesthesia type; (B) overall survival curves from the date of surgery by anesthesia type after propensity score matching. DES= desflurane, TIVA = total intravenous anesthesia.

3.3.5. Disease progression. Patients who received TIVA had less postoperative recurrence than those who received DES anesthesia. The crude HR was 0.28 (95% CI, 0.13–0.61; $P = .001$), and the PS-matched HR was 0.32 (95% CI, 0.14–0.75; $P = .009$). Patients who received TIVA had less postoperative metastasis than those who received DES anesthesia. The crude HR was 0.25 (95% CI, 0.10–0.62; $P = .003$), and the PS-matched HR was 0.31 (95% CI, 0.11–0.89; $P = .029$). Patients who received TIVA had less postoperative recurrence and metastasis than those who received DES anesthesia. The crude HR was 0.25 (95% CI, 0.10–0.63; $P = .003$), and the PS-matched HR was 0.31 (95% CI, 0.11–0.90; $P = .031$) (Table 3).

In summary, TIVA was associated with lower all-cause and cancer-specific mortality in patients undergoing limb-salvage surgery for OS. Patients with postoperative metastasis or TNM stage II to III had better outcomes in the TIVA group than those in the DES group. In addition, patients who received DES anesthesia had poorer disease progression than those who received TIVA.

4. Discussion

The main finding of this study was that propofol-based TIVA in limb-salvage surgery for OS improved survival and reduced the risks of postoperative recurrence and metastasis compared to

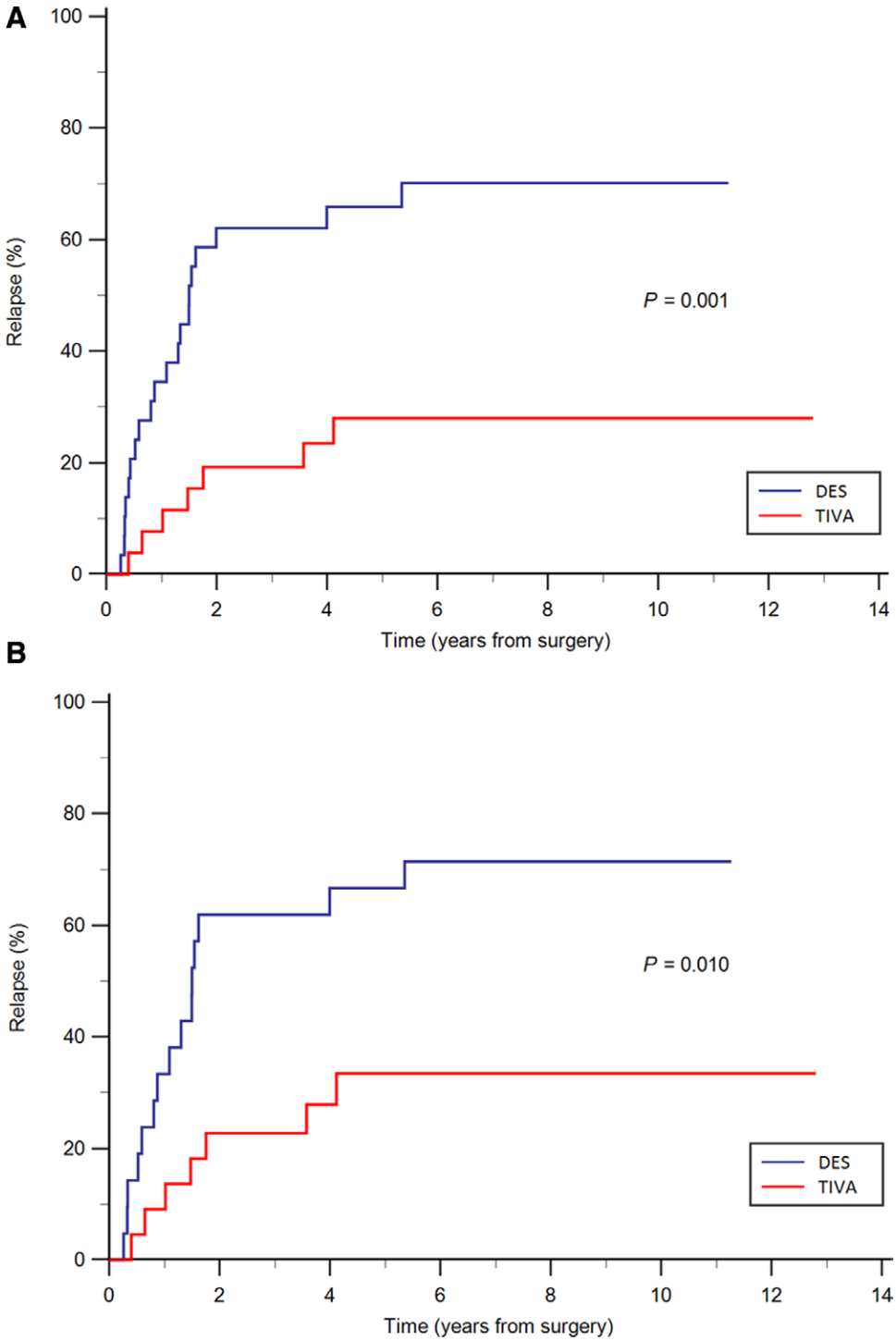

Figure 3. (A) Cumulative relapse curves from the date of surgery by anesthesia type; (B) cumulative relapse curves from the date of surgery by anesthesia type after propensity score matching. DES= desflurane, TIVA = total intravenous anesthesia.

DES anesthesia. Our results were consistent with previous studies demonstrating that TIVA was associated with better outcomes than VA in some solid cancers.[16–25] Nevertheless, retrospective studies have reported insignificant differences in survival outcomes between TIVA and VA in lung, breast, and digestive tract cancer surgeries.[27–30] Thus, the effects of anesthetic techniques on oncological outcomes from available data are still inconclusive.

Surgery is the mainstay of cancer treatment for potentially removable solid tumors. However, tumor cells may disseminate into the vascular and lymphatic systems during surgical manipulation and subsequently migrate to distant organs and initiate tumor regrowth.[4,5] Owing to the advancement in surgical techniques and chemoradiation treatment, survival rates in OS have increased to approximately 70% at the 5-year follow-up, and have reached a plateau over several decades.[1,2] Nevertheless, OS patients with metastatic or recurrent disease fare poorly, with overall survival rates of less than 20%.[1] Postoperative recurrence and metastasis play essential roles in survival, which makes it necessary to discover ways to improve long-term outcomes by reducing the incidence of relapse. The likelihood of metastatic recurrence depends on the balance between the metastatic potential of neoplasms and the anti-metastatic host

Table 2

Cox proportional hazards regression for mortality: univariate and multivariate models for overall patients.

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Anesthesia, TIVA (ref: DES)	0.20 (0.07–0.60)	.004	0.09 (0.02–0.36)	.001
Time since the earliest included patient (yr)	0.98 (0.84–1.14)	.765		
Sex (ref: female)	1.11 (0.47–2.65)	.807		
BMI (kg/m^2)	1.03 (0.92–1.14)	.656		
Charlson comorbidity index	1.43 (1.16–1.75)	.001	1.10 (0.66–1.83)	.710
ASA, III (ref: II)	3.48 (1.45–8.33)	.005	2.71 (0.43–17.0)	.287
Tumor location (ref: femur)				
Tibia	1.39 (0.52–3.73)	.516		
Humerus	1.08 (0.28–4.19)	.916		
Fibula	1.85 (0.38–8.91)	.444		
Tumor size (ref: <8 cm)	2.31 (0.98–5.45)	.056		
Pathologic fracture (ref: no)	0.68 (0.09–5.04)	.702		
ALP (ref: ≤129 IU/L)	7.58 (3.12–18.4)	<.001	9.16 (2.02–41.6)	.004
LDH (ref: ≤271 IU/L)	2.95 (1.22–7.14)	.016	0.72 (0.21–2.49)	.607
TNM stage, II–III (ref: I)	6.02 (1.40–26.0)	.016	6.27 (0.44–89.0)	.175
Neoadjuvant CT (ref: no)	2.48 (0.96–6.39)	.061		
Adjuvant CT (ref: no)	3.41 (1.15–10.2)	.027	0.71 (0.08–6.42)	.756
Adjuvant RT (ref: no)	3.41 (1.36–8.54)	.009	1.07 (0.26–4.37)	.930
Intraoperative transfusion (ref: no)	3.18 (1.34–7.58)	.009	0.57 (0.13–2.48)	.456
Postoperative NSAID (ref: no)	0.84 (0.36–1.98)	.687		
Operation time (min)	1.00 (0.99–1.01)	.220		
Anesthesia time (min)	1.00 (0.99–1.01)	.218		
Grade of surgical complications (ref: 0)				
I	0.53 (0.14–1.96)	.340		
II	2.28 (0.80–6.48)	.124		
Postoperative recurrence (ref: no)	35.3 (4.70–265)	.001		
Postoperative metastasis (ref: no)	48.3 (10.8–215)	<.001		

Notes: Hazard ratios in the multivariate analyses were adjusted by those variables having significance in the univariate analyses except recurrence and metastasis.

ALP = alkaline phosphatase, ASA = American Society of Anesthesiologists, BMI = body mass index, CT = chemotherapy, DES = desflurane, LDH = lactic dehydrogenase, NSAID = nonsteroid anti-inflammatory drug, RT = radiotherapy, TIVA = total intravenous anesthesia, TNM = tumor–node–metastasis.

defenses, of which cell-mediated immunity and natural killer cell function are decisive components.[6] Evidence from animal and human cancer cell line studies has shown that various anesthetics can affect the immune system in different ways, and may therefore influence cancer outcomes.[7–11]

In this study, we found a 70% lower mortality rate with TIVA than with DES anesthesia in patients after limb-salvage surgery for OS. In addition, TIVA was also shown to be associated with a reduced risk of postoperative recurrence and metastasis compared to DES anesthesia for patients with OS, comparable to results in patients undergoing surgeries for hepatocellular carcinoma, intrahepatic cholangiocarcinoma, glioblastoma, as well as colon, prostate, pancreatic, gastric, and ovarian cancer.[18–25] However, no study has compared the effects of TIVA and VA on patient outcomes after surgery for OS. Although our results imply a potential effect of anesthetics in humans, it seems biologically implausible that malignant potential of cancers can be reduced by such a large magnitude purely by anesthetic selection. Our results may overestimate the real treatment effect, which is a common bias in retrospective studies. Additionally, by contrast with propofol, INHAs have very slow terminal elimination from the vessel-rich group and even slower elimination from the whole body, especially in lengthy anesthesia.[36] Therefore, the exact time interval that INHAs act in cancer cells may be longer than the recorded anesthesia time. Of course, further investigations are warranted to determine the effects of anesthetic techniques on OS cell biology.

Concerning clinicopathological parameters associated with overall survival in patients having OS, elevated serum ALP level was another prognostic factor. This study showed that an increased preoperative ALP level was associated with poor survival for patients undergoing OS surgery, as reported previously.[32] Other variables, including high CCI, ASA physical status, elevated serum LDH level, late TNM stage, administration of adjuvant chemotherapy and radiotherapy, and intraoperative blood transfusion, were significantly associated with higher risks of overall mortality in the univariate Cox regression analysis, but insignificantly in the multivariate model.

Laboratory data from human OS cell lines support the influence of propofol on the behavior of OS cells through various pathways.[37–39] Using human OS cell lines, propofol was found to inhibit cell proliferation and invasion and promote apoptosis of OS cells by enhancing miR-143, which downregulates the expression of matrix metalloproteinase 13.[37] Xu et al[38] also demonstrated that propofol could suppress cell proliferation and invasion and induce apoptosis of OS cells through the downregulation of transforming growth factor-β1 expression. In a recent study, Huang et al[39] reported that propofol impeded cell proliferation, migration, and invasion of OS cells by regulating the FOXO1/TUSC7 axis to inactivate AKT/GSK3β signaling. Collectively, these findings imply that propofol possesses an anti-cancer ability and may be an effective anesthetic agent in OS surgery. In contrast, research on the impact of INHAs on OS cell biology is limited. From available published articles, sevoflurane was found to inhibit cell proliferation and invasion of OS cells by targeting the miR-203/WNT2B/Wnt/β-catenin axis and inactivating the PI3K/AKT pathway.[40,41] However, further studies are needed to clarify the influence of INHAs on OS cell biology due to the lack of data from DES and other INHAs.

Besides cellular signaling processes, the effect of anesthetics on the immune system is also an important pathway to determine tumorigenesis. In general, propofol increases cytotoxic T-lymphocyte activity, decreases pro-inflammatory cytokines, and inhibits cyclooxygenase-2 and prostaglandin E_2 functions; on the contrary, INHAs have been reported to suppress nature killer cell cytotoxicity, induce T-lymphocyte apoptosis, and decrease the T-helper 1/2 ratio.[5] The distinct effects on the immune system between propofol and INHAs may affect the

Table 3

Subgroup analyses for all-cause mortality, cancer-specific mortality, presence of postoperative recurrence, postoperative metastasis, TNM stage, and disease progression.

Stratified variable	Anesthesia	Crude HR (95% CI)	*P* value	*P* value (Interaction)	PS-matched HR (95% CI)	*P* value
All-cause mortality						
	DES	1.00			1.00	
	TIVA	0.20 (0.07–0.60)	.004		0.30 (0.11–0.81)	.018
Cancer-specific mortality						
	DES	1.00			1.00	
	TIVA	0.20 (0.07–0.60)	.004		0.30 (0.11–0.81)	.018
Postoperative recurrence				.941		
No	DES	Cannot converge			Cannot converge	
	TIVA					
Yes	DES	1.00			1.00	
	TIVA	0.53 (0.21–1.38)	.197		0.65 (0.22–1.89)	.426
Postoperative metastasis				.950		
No	DES	Cannot converge			Cannot converge	
	TIVA					
Yes	DES	1.00			1.00	
	TIVA	0.25 (0.08–0.78)	.017		0.24 (0.06–0.87)	.030
TNM stage				.950		
I	DES	Cannot converge			Cannot converge	
	TIVA					
II–III	DES	1.00			1.00	
	TIVA	0.17 (0.07–0.44)	<.001		0.26 (0.09–0.73)	.011
Disease progression						
Postoperative recurrence	DES	1.00			1.00	
	TIVA	0.28 (0.13–0.61)	.001		0.32 (0.14–0.75)	.009
Postoperative metastasis	DES	1.00			1.00	
	TIVA	0.25 (0.10–0.62)	.003		0.31 (0.11–0.89)	.029
Postoperative recurrence + metastasis	DES	1.00			1.00	
	TIVA	0.25 (0.10–0.63)	.003		0.31 (0.11–0.90)	.031

CI = confidence interval, DES = desflurane, HR = hazard ratio, PS = propensity score, TIVA = total intravenous anesthesia, TNM = tumor–node–metastasis.

level of surgery-induced immunosuppression and subsequent cancer progression. Conclusively, the mechanisms of anesthetics contributing to the progression of OS cells are mainly supposed to directly affect signaling pathways of cancer cells and indirectly influence neuroendocrine and immune function.

There were some limitations in the present study. First, because this was a single-center observational cohort study, our results could not conclude the causal relationship between anesthetic techniques and oncological outcomes after OS surgery and should be only deemed as hypothesis-generating. Second, the study was retrospective, and patients were not randomly allocated. PS matching was done to minimize confounding in this observational study,[35] but the small size of the groups may have influenced the reliability of statistical significance in our study. Third, although performing the multivariate and PS matching analysis with many variables to obtain reliable results, we could not exclude some unmeasured confounding factors that may be responsible for the results. Fourth, because of unavailable detailed information about surgical techniques and cancer care, we could not completely exclude the possibility that advances in cancer care and surgical techniques may influence survival outcomes. Fifth, we included only DES in our analysis because it is the most frequently used INHA in our hospital; however, different INHAs may have distinctive effects on OS. Sixth, we analyzed only the diagnosis of OS, accounting for the majority of primary bone malignancies,[3] and did not refine the histologic subtypes due to incomplete data. Finally, we excluded OS patients undergoing amputation surgery (n = 11) to increase the consistency of patient characteristics, and limb-salvage surgery was reported to be associated with a higher 5-year overall survival.[42] Despite these limitations, our results may have an important clinical implication for OS management if the relationship between anesthetic techniques and oncological outcomes after cancer surgery is indeed causal.

5. Conclusion

Propofol-based TIVA was associated with better survival than DES anesthesia in limb-salvage surgery for OS. TIVA also showed better outcomes in OS patients with postoperative metastasis or with TNM stage II to III compared to DES anesthesia. In addition, patients who were administered with TIVA had significantly lower risks of postoperative recurrence and metastasis.

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