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Original Article

Long-term oncologic outcomes of breast conserving surgery with propofol-based total intravenous anesthesia or volatile inhalational general anesthesia without propofol: a propensity score-matched, population-based cohort study

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Abstract: To estimate oncologic outcomes (overall survival [OS], locoregional recurrence [LRR], and distant metastasis [DM]) in patients with breast intraductal carcinoma (IDC) receiving breast conserving surgery (BCS) under propofol-based total intravenous anesthesia (TIVA) or volatile inhalational (INHA) general anesthesia (GA) without propofol. Patients with breast IDC receiving BCS were recruited through propensity score matching and categorized by anesthesia techniques into propofol-based TIVA-GA and non-propofol-based INHA-GA groups, respectively. Cox regression analysis was performed to calculate hazard ratios and 95% confidence intervals (CIs). In multivariate Cox regression analysis, the adjusted hazard ratio (aHR; 95% CI) of all-cause mortality for TIVA-GA with propofol compared with INHA-GA without propofol was 0.94 (0.83-1.31). The aHR (95% CI) of LRR for TIVA-GA with propofol group compared with INHA-GA without propofol was 0.77 (0.58-0.87). The aHR (95% CI) of DM for TIVA-GA with propofol compared with INHA-GA without propofol was 0.91 (0.82-1.24). Propofol-based TIVA-GA might be beneficial for reducing LRR in women with breast IDC receiving BCS compared with non-propofol-based INHA-GA.

Keywords: Breast intraductal carcinoma, breast conserving surgery, propofol, general anesthesia, survival

Introduction

The possibility of anesthetic drugs and techniques affecting the risk of cancer recurrence is of particular importance to patients and their clinicians [1-4]. Between 2008 and 2018, the number of cancer cases increased by over 25% globally and in Taiwan [5-7], and nearly two-thirds of patients diagnosed with cancer undergo anesthesia and surgery for curative or palliative first-line treatment [8]. Thus, the effects of anesthesia on oncologic outcomes can considerably affect the health of this population.

Laboratory studies have suggested some potential mechanisms through which volatile anesthetics enhance metastasis including the direct survival-enhancing effects of volatile agents on cancer cells and the suppression of immune cell function and tumor cell apoptosis [1-4]. However, molecular mechanisms underlying such effects are incompletely understood,

and conflicting evidence exists for inhaled agents and cancer cell lines [9-12].

Clinical studies (most retrospective) comparing intravenous and volatile inhalational (INHA) agents for general anesthesia (GA) have reported mixed results, with some showing a beneficial effect of propofol-based total intravenous anesthesia (TIVA)-GA and others showing no effect compared with inhaled anesthetics [13-21]. Large, prospective, randomized controlled trials (RCTs) focusing on the extent of surgery, local anesthesia, or GA are required to prove a causal relationship between anesthetic techniques and long-term oncologic outcomes. To date, no head-to-head propensity score matching (PSM) study with a large sample and a long-term follow-up has estimated oncologic outcomes (overall survival [OS], locoregional recurrence [LRR], and distant metastasis [DM]) in patients with breast intraductal carcinoma (IDC) receiving breast conserving surgery (BCS) with propofol-based TIVA-GA or non-propofol-based INHA-GA. Therefore, we performed a head-to-head PSM study to estimate long-term oncologic outcomes, namely OS, LRR, and DM, in patients with breast IDC receiving BCS under propofol-based TIVA-GA or non-propofol-based INHA-GA.

Patients and methods

Study cohorts

We established a cohort comprising female patients with breast IDC by using data from the Taiwan Cancer Registry Database (TCRD), which is maintained by the Collaboration Center of Health Information Application. We enrolled patients who received a diagnosis of IDC between January 1, 2009, and December 31, 2018, and underwent BCS. The follow-up duration was from the index date to December 31, 2019. The index date was the date of BCS. The mean follow-up durations were 63.5 months (standard deviation [SD], 29.7 months) and 61.8 months (29.4 months) in the propofol-based TIVA and non-propofol-based INHA groups, respectively. The TCRD contains detailed cancer-related information including the stage (according to the American Joint Committee on Cancer [AJCC], seventh edition), treatment modalities, pathologic data (including the pathologic stage), radiation doses, hormone receptor (HR) status, human epidermal growth factor receptor-2 (HER2) status, radiotherapy (RT) regimens, and chemotherapy regimens [22-27]. Our study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B). Patient diagnoses were confirmed on the basis of pathologic data, and patients who received a new diagnosis of IDC were confirmed to have no other cancers. In the propofol-based TIVA group, separate infusions of propofol (approximately 3 mg/kg/h) and remifentanil (0.5 μg/kg/min) were immediately started after the intravenous induction of anesthesia. The mean dosage of propofol was 811.2 mg in the TIVA group [28]. In the INHA group, anesthesia was maintained with sevoflurane in 100% oxygen at a flow rate of ≥5 L/min in a circle system, with an end-tidal concentration of sevoflurane at a minimum alveolar concentration of approximately ≥2 [29]. Other inclusion criteria were age ≥20 years and pathologic AJCC stage I-IV. Patients who developed metastasis, had missing sex data, were aged <20 years, received nonstandard adjuvant breast RT (i.e., other than standard adjuvant RT consisting of irradiation to both the chest wall/whole breast and regional nodes with a minimum of 50 Gy), received neoadjuvant chemotherapy, had unclear differentiation of the tumor grade, had missing HR status, had missing HER2 status, or had unclear staging were excluded. Adjuvant treatments such as adjuvant RT, adjuvant chemotherapy, hormone therapy, and target therapy was allowed on the basis of National Comprehensive Cancer Network (NCCN) guidelines in Taiwan [30]. Furthermore, we excluded patients with unclear surgical procedures, poorly defined nodal surgery, unclear HR status, unclear Her-2 status, unknown pathologic stages, unknown American Society of Anesthesiology (ASA) physical status, unclear Charlson comorbidity index (CCI), unclear differentiation, or nonrecorded hospital type [31] (academic center or community hospital). HR positivity was defined as ≥1% of tumor cells demonstrating positive nuclear staining through immunohistochemistry [32], and HER2 positivity was defined as an immunohistochemistry score of 3+ or a fluorescence in situ hybridization ratio of ≥2 [31, 33]. Finally, we enrolled patients with IDC who received BCS under TIVA with propofol or INHA without propofol for perioperative anesthesia. Comorbidities were assessed using the CCI [34, 35]. The CCI has prognostic significance for all-cause mortality in patients with breast cancer [36, 37]. Only comorbidities observed 6 months before the index date were included, and new-onset comorbidities that

were diagnosed within 6 months before the index date were excluded. Thus, on the basis of this inclusion criterion, we could analyze the effect of long-term comorbidities on survival. Comorbidities were identified according to primary *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes; diseases present at the first admission and those identified more than twice during outpatient visits were included as comorbidities.

PSM and covariates

After adjustment for confounders, a Cox proportional hazard model was established to model the time from the index date to all-cause mortality, LRR, and DM for patients with IDC. We performed PSM to reduce the effects of potential confounders when oncologic outcomes between different anesthesia groups were compared. The matching variables were age, menopausal status, diagnosis year, CCI score, differentiation, pathologic stage, pathologic tumor (pT) stage, pathologic nodal (pN) stage, ASA physical status, adjuvant chemotherapy, adjuvant RT, HR status, Her-2 status, nodal surgery, and hospital level. We matched the cohorts at a ratio of 1:1 by using the greedy method with age, diagnosis year, menopausal status, pathologic stage, and adjuvant RT completely matched and the propensity score being within a caliper of 0.2 [38]. Matching is a common technique used for selecting controls with background covariates identical to those of study participants to minimize differences between individuals. A Cox model was used to regress all-cause mortality, LRR, and DM for the different anesthesia statuses, and a robust sandwich estimator was used to account for clustering within matched sets [39]. Multivariate Cox regression analysis was performed to calculate hazard ratios to determine whether factors such as anesthesia type, age, menopausal status, diagnosis year, CCI score, differentiation, pathologic stage, pT stage, pN stage, ASA physical status, adjuvant chemotherapy, adjuvant RT, HR status, Her-2 status, nodal surgery, and hospital level are potential independent predictors of all-cause mortality, LRR, or DM. Potential predictors were controlled for in the analysis (**Table 1**), and all-cause mortality was the primary endpoint in both anesthesia groups. We supplied the characteristics of our patients before PSM as Supplementary Table 1 to indicate the extent of compensation made by PSM. Moreover, we also have supplied the Distribution of propensity score before and after matching as Supplementary Figure 1 to test the quality of PSM.

Statistics

Continuous variables are expressed as mean ± SD. Comparisons among the 2 groups were conducted using independent t-test for continuous variables, analysis of variance for more than two continuous variables, and a Chi-square test for categorical variables. Cox proportional hazard curves were plotted to estimate all-cause mortality (i.e., OS) in patients with breast IDC receiving BCS. Covariates in the TIVA-GA with propofol group were 1:1 matched to those in the INHA-GA without propofol group through PSM with replacement, and all matched covariates in the TIVA-GA with propofol and INHA-GA without propofol groups were included in the Cox proportional hazards model. After adjustment for confounders, the Cox proportional hazards method was used to model the time from the index date to all-cause mortality. In the multivariate analysis, hazard ratios were adjusted for anesthesia type, age, menopausal status, diagnosis year, CCI score, differentiation, pathologic stage, pT stage, pN stage, ASA physical status, adjuvant chemotherapy, adjuvant RT, HR status, Her-2 status, nodal surgery, and hospital level. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). In a two-tailed Wald test, $P<0.05$ was considered significant. OS, LRR-free survival, and DM-free survival were estimated using the Kaplan-Meier method, and differences between the two GA modalities were determined using the stratified log-rank test to compare survival curves (stratified according to matched sets) [40].

Results

PSM and study cohort

The matching process yielded a final cohort of 3868 patients (1934 and 1934 in the TIVA-GA with propofol and INHA-GA without propofol groups, respectively) who were eligible for further analysis; their characteristics are summarized in **Table 1**. Age distribution was balanced between the two groups (**Table 1**). Menopausal status, diagnosis year, CCI score, differentiation, pathologic AJCC stage, pT stage, pN stage, hospital level, adjuvant RT, adjuvant chemo-

Table 1. Demographics of propensity score-matched patients with breast cancer receiving breast conserving surgery undergoing TIVA-GA with propofol or INHA-GA without propofol

		TIVA-GA with Propofol N=1934	INHA-GA without Propofol N=1934	P
		N (%)	n (%)	
Age, years	Mean (SD)	54.6 (11.8)	54.6 (11.8)	0.6511*
	Median (IQR, Q1-Q3)	54 (46-63)	54 (46-63)	
	20-49	690 (35.7)	690 (35.7)	1.0000#
	50+	1244 (64.3)	1244 (64.3)	
Diagnosis year	2009-2013	300 (15.5)	300 (15.5)	1.0000#
	2014-2018	1634 (84.5)	1634 (84.5)	
Menopausal status	Premenopausal	682 (35.3)	682 (35.3)	1.0000#
	Postmenopausal	1252 (64.8)	1252 (64.8)	
CCI Score	0	1262 (65.3)	1310 (67.7)	0.0452#
	1	406 (21.0)	385 (19.9)	
	2+	266 (13.8)	239 (12.4)	
Differentiation	I	387 (20.0)	389 (20.1)	0.3469#
	II	988 (51.1)	1014 (52.4)	
	III	559 (28.9)	531 (27.5)	
AJCC Pathologic stage	I	767 (39.6)	767 (39.6)	1.0000#
	II	863 (44.6)	863 (44.6)	
	III	304 (15.7)	304 (15.7)	
pT	pT1	911 (47.1)	919 (47.5)	0.4645#
	pT2	888 (45.9)	893 (46.2)	
	pT3-4	135 (7.0)	122 (6.3)	
pN	pN0	1258 (65.0)	1260 (65.1)	0.8901#
	pN1	416 (21.5)	418 (21.6)	
	pN2-3	260 (13.4)	256 (13.2)	
ASA physical status	ASA I	1087 (56.2)	1108 (57.3)	0.2782#
	ASA II	451 (23.3)	461 (23.8)	
	ASA III-IV	396 (20.5)	365 (18.9)	
Adjuvant chemotherapy	No	697 (36.0)	685 (35.4)	0.5382#
	Yes	1237 (64.0)	1249 (64.6)	
Adjuvant RT	No	186 (10.0)	186 (10.0)	1.0000#
	Yes	1748 (90.0)	1748 (90.0)	
Hormone Receptor	No	952 (49.2)	945 (48.9)	0.7260#
	Yes	982 (50.8)	989 (51.1)	
Her-2 receptor	No	1691 (87.4)	1685 (87.1)	0.7218#
	Yes	243 (12.6)	249 (12.9)	
Nodal surgery	ALND	619 (32.0)	622 (32.2)	0.8795#
	SLNB	1315 (68.0)	1312 (67.8)	
Hospital level	Academic center	1618 (83.7)	1609 (83.2)	0.4781#
	Nonacademic center	316 (16.3)	325 (16.8)	
Follow-up time, months	Mean (SD)	63.5 (29.7)	61.8 (29.4)	
Death		140 (7.2)	203 (10.5)	0.0616#
Locoregional recurrence		87 (4.5)	154 (8.0)	0.0001#
Distant metastasis		175 (9.0)	255 (13.2)	0.0212#

IQR, interquartile range; TIVA, total intravenous anesthesia; GA, general anesthesia; INHA, inhalational; SD, standard deviation; AJCC, American Joint Committee on Cancer; Her-2, Human Epidermal Growth Factor Receptor-2; RT, radiotherapy; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy. #*P* value was estimated using the chi-square test; **P* value was estimated using independent t-test.

therapy, ASA physical status, HR status, Her-2 status, and nodal surgery were similar after head-to-head PSM in the two cohorts, and no significant differences were observed in any variable between the cohorts. The follow-up duration, LRR, DM, and all-cause mortality were not matched because oncologic outcomes were inconsistent between the two groups (**Table 1**). The crude outcomes of DM and LRR in women with breast cancer receiving BCS undergoing TIVA with propofol or INHA without propofol varied significantly (**Table 1**).

Prognostic factors for all-cause mortality after multivariate Cox regression analysis

The results of multivariate Cox regression analysis indicated that adjuvant chemotherapy, adjuvant RT, and HR positivity were favorable prognostic factors for OS (**Table 2**). No significant differences were observed in the explanatory variables, except for a CCI of ≥2, differentiation grade III (poor differentiation), pathologic stage III, pT2, pT3-4, pN1, pN2-3, Her-2 positivity, adjuvant chemotherapy, adjuvant RT, and HR positivity (**Table 2**). In the multivariate Cox regression analysis, the adjusted hazard ratio (aHR; 95% confidence interval [CI]) of all-cause mortality for the TIVA-GA with propofol group compared with the INHA-GA without propofol group was 0.94 (0.83-1.31). The aHRs (95% CIs) of all-cause mortality for a CCI of ≥2, differentiation grade III, pathologic stage III, pT2, pT3-4, pN1, pN2-3, and Her-2 positivity were 1.78 (1.24-2.57), 1.80 (1.21-2.67), 1.56 (1.01-2.41), 1.93 (1.43-2.60), 2.60 (1.74-3.89), 1.63 (1.20-2.21), 3.35 (2.40-4.68), and 1.51 (1.14-2.00), respectively, compared with a CCI of 0, differentiation grade I, pathologic stage I, pT1, pT1, pN0, pN0, and Her-2 negativity, respectively. The aHRs (95% CIs) of all-cause mortality for adjuvant chemotherapy, adjuvant RT, and HR positivity were 0.51 (0.39-0.65), 0.56 (0.43-0.74), and 0.77 (0.61-0.98), respectively, compared with no adjuvant chemotherapy, no adjuvant RT, and HR negativity, respectively.

Prognostic factors for LRR after multivariate Cox regression analysis

The aHR (95% CI) of LRR for the TIVA-GA with propofol group compared with the INHA-GA without propofol group was 0.77 (0.58-0.87) (**Table 3**). The aHRs (95% CIs) of LRR for differentiation grade II, grade III, pathologic stage II, stage III, pT3-4, pN2-3, and Her-2 positivity were 1.65 (1.07-2.55), 1.99 (1.24-3.19), 1.65 (1.16-2.36), 2.27 (1.31-3.95), 1.22 (1.09-2.14), 1.22 (1.07-1.88), and 2.18 (1.55-3.07), respectively, compared with differentiation grade I, differentiation grade I, pathologic stage I, pathologic stage I, pT1, pN0, and HER-2 negativity, respectively. The aHR (95% CI) of LRR for adjuvant RT compared with no adjuvant RT was 0.69 (0.48-0.99).

Prognostic factors for DM after multivariate Cox regression analysis

The aHR (95% CI) of DM for the TIVA-GA with propofol group compared with the INHA-GA without propofol group was 0.91 (0.82-1.24) (**Table 4**). The aHR of DM for differentiated grade II, differentiated grade III, pathologic stage III, pT2, pT3-4, pN1, pN2-3, and Her-2 positivity were 1.92 (1.31-2.81), 2.52 (1.69-3.76), 1.72 (1.17-2.52), 1.47 (1.15-1.87), 1.76 (1.20-2.57), 1.32 (1.01-1.73), 2.40 (1.76-3.26), and 3.01 (2.39-3.79), respectively, compared with differentiated grade I, differentiated grade I, pathologic stage I, pT1, pT1, pN0, pN0, and HER-2 negativity. The aHR of DM for adjuvant chemotherapy compared with no adjuvant chemotherapy was 0.55 (0.43-0.71).

Differences in Kaplan-Meier OS, LRR-free survival, and DM-free survival curves between TIVA-GA with propofol and INHA-GA without propofol

Figure 1A-C presents survival curves for OS, LRR-free survival, and DM-free survival obtained using the Kaplan-Meier method for the TIVA-GA with propofol and INHA-GA without propofol groups. The LRR-free survival for the TIVA-GA with propofol group was higher than that for the INHA-GA without propofol group for all patients with breast IDC receiving BCS (P=0.0189).

Discussion

In 2019, a meta-analysis of six studies (five retrospective studies and one small RCT) including over 7800 patients who underwent surgery for breast cancer, esophageal cancer, or non-small-cell lung cancer found that the use of TIVA-GA was associated with improved recurrence-free survival compared with INHA-GA (pooled hazard ratio =0.78, 95% CI=0.65-0.94)

Table 2. Multivariate analysis of all-cause death for propensity score-matched patients with breast cancer receiving breast conserving surgery under TIVA-GA with propofol or INHA-GA without propofol

		All-cause Mortality	
		aHR* (95% CI)	P
Anesthesia	Nonpropofol	Ref	0.7457
	Propofol	0.94 (0.83-1.31)	
Age, years	20-49	ref	0.1556
	50+	1.24 (0.92-1.65)	
Diagnosis year	2009-2013	ref	0.2064
	2014-2018	0.84 (0.64-1.10)	
Menopausal status	Premenopausal	ref	0.6510
	Postmenopausal	0.89 (0.85-1.55)	
CCI Scores	0	ref	0.0055
	1	1.18 (0.85-1.64)	
	2+	1.78 (1.24-2.57)	
Differentiation	I	ref	0.0007
	II	1.19 (0.82-1.73)	
	III	1.80 (1.21-2.67)	
AJCC Pathologic stage	I	ref	0.0062
	II	0.93 (0.67-1.30)	
	III	1.56 (1.01-2.41)	
pT	pT1	ref	<0.0001
	pT2	1.93 (1.43-2.60)	
	pT3-4	2.60 (1.74-3.89)	
pN	pN0	ref	<0.0001
	pN1	1.63 (1.20-2.21)	
	pN2-3	3.35 (2.40-4.68)	
Nodal surgery	ALND	ref	0.2523
	SLNB	0.90 (0.63-1.29)	
ASA	I	ref	0.3427
	II	0.95 (0.69-1.32)	
	III-IV	1.19 (0.83-1.72)	
Adjuvant chemotherapy		0.51 (0.39-0.65)	<0.0001
Adjuvant RT		0.56 (0.43-0.74)	<0.0001
HR positive		0.77 (0.61-0.98)	0.0342
Her-2 positive		1.51 (1.14-2.00)	0.0038
Hospital level	Academic center	ref	0.3225
	Nonacademic center	1.15 (0.87-1.53)	

TIVA, total intravenous anesthesia; GA, general anesthesia; INHA, inhalational; aHR, adjusted hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; HR, Hormone Receptor; Her-2, Human Epidermal Growth Factor Receptor-2; RT, radiotherapy; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy. *All covariates mentioned in **Table 2** were adjusted. A two-tailed *P*-value of <0.05 was considered statistically significant.

[41]. However, interpretation of these results is limited by heterogeneity with respect to the extent of surgery, cancer types, and patient characteristics as well as other limitations associated with retrospective studies [41]. However, a subsequent retrospective Danish database analysis of over 8600 propensity score-matched patients undergoing surgery for colorectal cancer revealed a small increase in cancer recurrence in non-propofol-based INHA-GA compared with propofol-based TIVA-GA (hazard ratio =1.12, 95% CI=1.02-1.13) [42]. No difference in the OS of patients with colorectal cancer was observed between propofol-based TIVA-GA and non-propofol-based INHA-GA [42]. Until now, no large, prospective, RCT has addressed this crucial topic for patients with breast IDC receiving BCS under propofol-based TIVA-GA or non-propofol-based INHA-GA. Proving a causal relationship between anesthetic techniques and long-term oncologic outcomes can be valuable for patients with breast IDC receiving BCS. In this current study, we estimated the long-term oncologic outcomes of women with breast IDC receiving BCS under propofol-based TIVA-GA or non-propofol-based INHA-GA.

TIVA-GA employs a sedative-hypnotic anesthetic (propofol) and an analgesic component (typically an opioid agent) [17, 42]. The advantage of propofol-based TIVA-GA is that the propofol and opioid agent exert a weaker effect on evoked potentials than potent do volatile inhalation agents or nitrous oxide [43, 44]. In particular, motor evoked potentials are sensitive to inhalation agents, whereas somatosensory evoked poten-

Table 3. Multivariate analysis of locoregional recurrence for propensity score-matched patients with breast cancer receiving breast conserving surgery under TIVA-GA with propofol or INHA-GA without propofol

		Locoregional Recurrence	
		aHR* (95% CI)	P
Anesthesia	Nonpropofol	ref	0.0303
	Propofol	0.77 (0.58-0.87)	
Age, years	20-49	ref	0.3127
	50+	0.68 (0.50-1.12)	
Diagnosis year	2009-2013	ref	0.1340
	2014-2018	0.79 (0.58-1.08)	
Menopausal status	Premenopausal	ref	0.7192
	Postmenopausal	0.93 (0.72-1.31)	
CCI scores	0	ref	0.6612
	1	1.02 (0.69-1.51)	
	2+	0.81 (0.47-1.39)	
Differentiation	I	ref	0.0170
	II	1.65 (1.07-2.55)	
	III	1.99 (1.24-3.19)	
AJCC pathologic stage	I	ref	0.0061
	II	1.65 (1.16-2.36)	
	III	2.27 (1.31-3.95)	
pT	pT1	ref	0.0206
	pT2	1.04 (0.62-1.15)	
	pT3-4	1.22 (1.09-2.14)	
pN	pN 0	ref	0.0162
	pN1	0.80 (0.55-1.16)	
	pN2-3	1.22 (1.07-1.88)	
Nodal surgery	ALND	ref	0.5720
	SLNB	0.95 (0.66-1.36)	
ASA	I	ref	0.9025
	II	1.02 (0.69-1.49)	
	III-IV	1.11 (0.70-1.75)	
Adjuvant chemotherapy		0.94 (0.69-1.29)	0.7178
Adjuvant RT		0.69 (0.48-0.99)	0.0443
HR positive		1.14 (0.85-1.52)	0.3847
Her-2 positive		2.18 (1.55-3.07)	<0.0001
Hospital level	Academic center	ref	0.5298
	Nonacademic center	1.12 (0.79-1.60)	

TIVA, total intravenous anesthesia; GA, general anesthesia; INHA, inhalational; aHR, adjusted hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; HR, Hormone Receptor; Her-2, Human Epidermal Growth Factor Receptor-2; RT, radiotherapy; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy. *All covariates mentioned in **Table 2** were adjusted. A two-tailed *P*-value of <0.05 was considered statistically significant.

tials are moderately affected [43, 44]. However, TIVA anesthetic techniques are typically more costly than inhalation techniques, depending on the selection of specific IV agents [45, 46]. Until now, no guidelines are available for choosing propofol-based TIVA-GA or INHA-GA without propofol for women with breast IDC receiving BCS.

As shown in **Table 1**, no bias was observed in the covariates for OS after head-to-head PSM in women with breast IDC receiving BCS under propofol-based TIVA-GA or non-propofol-based INHA-GA. After the Cox proportional multivariate analysis of all-cause mortality, independent poor prognostic factors for OS were a CCI of ≥2, differentiated grade 3, pathologic stage III, pT3-4, pN1, pN2-3, and HER-2 positivity (**Table 2**). These independent poor prognostic factors for OS are compatible with those reported in previous studies [23, 25-27]. High CCI [47, 48], poor differentiation [49], advanced pathologic stage, advanced pT stage, advanced pN stage, and Her-2 positivity [50] increased the risk of all-cause mortality; this finding was in accordance with those of previous studies [23, 25-27]. Moreover, as shown in **Table 2**, adjuvant chemotherapy [51], adjuvant RT [52], and HR positivity [53, 54] were better independent prognostic factors for OS; this result is compatible with those of previous studies [51-54]. The type of GA was not associated with OS in women with breast IDC receiving BCS. Our findings regarding OS are in agreement with those of previous studies [15, 18, 19]; we did not observe an association between the type of GA used

Table 4. Multivariate analysis of distant metastasis for propensity score-matched patients with breast cancer receiving breast conserving surgery under TIVA-GA with propofol or INHA-GA without propofol

		Distant Metastasis	
		aHR* (95% CI)	P
Anesthesia	Nonpropofol	ref	0.9126
	Propofol	0.91 (0.82-1.24)	
Age, years	20-49	ref	0.4894
	50+	0.92 (0.73-1.16)	
diagnosis year	2009-2013	ref	0.3106
	2014-2018	0.74 (0.58-1.13)	
Menopausal status	Premenopausal	ref	0.4541
	Postmenopausal	0.77 (0.64-1.11)	
CCI Scores	0	ref	0.4672
	1	1.18 (0.90-1.56)	
	2+	1.04 (0.72-1.52)	
Differentiation	I	ref	<0.0001
	II	1.92 (1.31-2.81)	
	III	2.52 (1.69-3.76)	
AJCC Pathologic stage	I	ref	0.0028
	II	1.04 (0.79-1.38)	
	III	1.72 (1.17-2.52)	
pT	pT1	ref	0.0020
	pT2	1.47 (1.15-1.87)	
	pT3-4	1.76 (1.20-2.57)	
pN	pN0	ref	<0.0001
	pN1	1.32 (1.01-1.73)	
	pN2-3	2.40 (1.76-3.26)	
Nodal surgery	ALND	ref	0.1819
	SLNB	1.27 (0.94-1.70)	
ASA	I	ref	0.3805
	II	0.85 (0.64-1.13)	
	III-IV	1.03 (0.74-1.44)	
Adjuvant chemotherapy		0.55 (0.43-0.71)	<0.0001
Adjuvant RT		0.94 (0.74-1.20)	0.6034
HR positive		1.06 (0.85-1.32)	0.5889
Her-2 positive		3.01 (2.39-3.79)	<0.0001
Hospital level	Academic center	ref	0.6442
	Nonacademic center	1.06 (0.82-1.39)	

TIVA, total intravenous anesthesia; GA, general anesthesia; INHA, inhalational; aHR, adjusted hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; HR, Hormone Receptor; Her-2, Human Epidermal Growth Factor Receptor-2; RT, radiotherapy; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy. *All covariates mentioned in **Table 2** were adjusted. A two-tailed *P*-value of <0.05 was considered statistically significant.

and the long-term prognosis of patients with breast cancer (**Table 2** and **Figure 1A**), although the extent of surgery in these studies was different. Nevertheless, some conclusions of previous studies were different from ours; previous studies have indicated that propofol may have a survival advantage compared with sevoflurane among patients with breast cancer [20, 21]. However, these studies did not provide clear information regarding cancer stages or the extent of surgery and they included insufficiently small samples [15, 18-21]. Only one retrospective study including a small sample size and a short-term follow-up duration focused on patients with breast cancer receiving modified radical mastectomy under propofol-based TIVA-GA or sevoflurane-based INHA-GA [15]. In our study, we included women with breast IDC receiving BCS under propofol-based TIVA-GA or non-propofol-based INHA-GA after head-to-head PSM (**Table 1**) and a long-term follow-up duration. This is the first and largest head-to-head PSM study to report no significant differences in OS between propofol-based TIVA-GA and non-propofol-based INHA-GA in patients with breast IDC receiving BCS (**Table 2** and **Figure 1A**). Although many preclinical studies have demonstrated various antitumor effects of propofol on different cancer cell lines [1-4], the clinical data remain controversial [13-21], particularly for different cancer types. These potential differences between preclinical and clinical studies might be because adjuvant treatments such as adjuvant chemotherapy and RT would have been indicated for women with breast IDC receiving BCS with risk factors in our

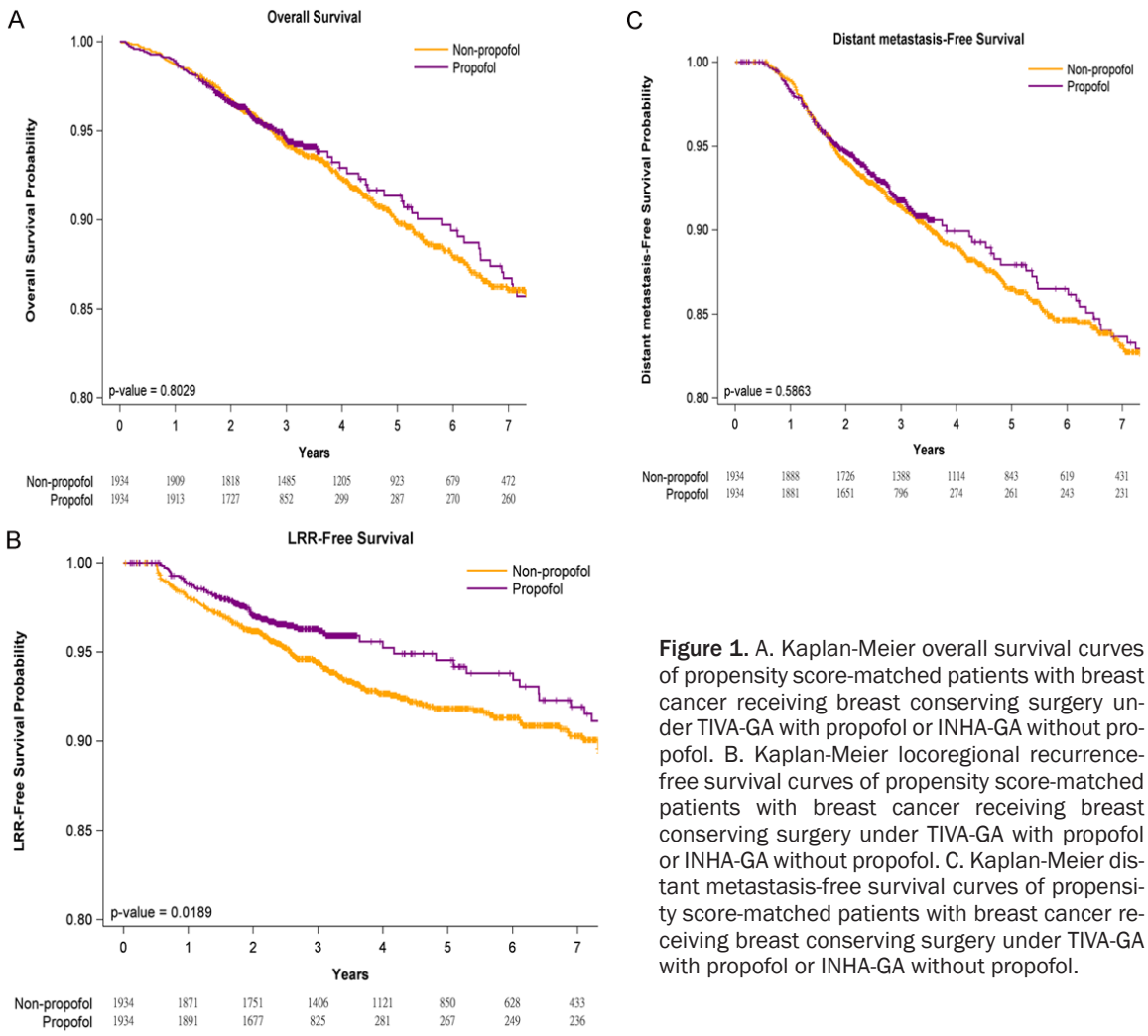

Figure 1. A. Kaplan-Meier overall survival curves of propensity score-matched patients with breast cancer receiving breast conserving surgery under TIVA-GA with propofol or INHA-GA without propofol. B. Kaplan-Meier locoregional recurrence-free survival curves of propensity score-matched patients with breast cancer receiving breast conserving surgery under TIVA-GA with propofol or INHA-GA without propofol. C. Kaplan-Meier distant metastasis-free survival curves of propensity score-matched patients with breast cancer receiving breast conserving surgery under TIVA-GA with propofol or INHA-GA without propofol.

clinical study according to NCCN guidelines [30]. In Taiwan, oncologists administer adjuvant treatments for patients with breast IDC based on NCCN guidelines [15, 18-21]. The benefit of OS in our clinical study might be masked by adjuvant treatments based on treatments guidelines.

The use of propofol-based anesthesia has been a topic of debate in terms of the recurrence rate in patients with breast IDC. An RCT showed that regional anesthesia-analgesia (paravertebral block and propofol) did not reduce breast cancer recurrence after potentially curative surgery compared with volatile anesthesia (sevoflurane) and opioids [55]. However, regional anesthesia with propofol-based analgesia was administered instead of GA with propofol-based TIVA-GA [55]. In addition, the definition of breast cancer recurrence included LRR and DM instead of LRR only [55]. The benefit in terms of the reduction of breast cancer recurrence for propofol-based anesthesia could not be distinguished from LRR or DM in the RCT [55]. Similarly, our study results showed no benefits in terms of the reduction of DM for patients with breast IDC receiving BCS under propofol-based TIVA-GA (**Table 4** and **Figure 1C**). Moreover, the dosage of propofol was different between regional anesthesia and TIVA-GA. The dosage of propofol in TIVA-GA was significantly higher than that in regional anesthesia with propofol. Therefore, this is the first clinical study to show a significant benefit of reduced LRR in women with breast IDC receiving BCS under propofol-based TIVA-GA compared with non-propofol-based INHA-GA (**Table 3** and **Figure 1B**). Other independent poor prognostic factors for LRR (**Table 3**) were differentiated grade II and III [15, 18-21, 56], pathologic

stage II and III, pT3-4, pN2-3, and Her-2 positivity [57]; this finding is compatible with those of previous studies [15, 18-21]. Adjuvant RT [52, 56] and propofol-based TIVA-GA were identified as better prognostic factors for LRR. Many studies have reported that adjuvant RT was beneficial in reducing LRR in patients with breast IDC receiving BCS [15, 18-21, 52, 56]. Similarly, our findings showed that adjuvant RT was beneficial in reducing LRR in patients with breast IDC receiving BCS (**Table 3**). This is the first study to show that, compared with non-propofol-based INHA-GA, propofol-based TIVA-GA might be associated with a reduction in the risk of LRR in women with breast IDC receiving BCS. This might be attributed to the finding of a clinical study that propofol exerts antitumor effects by directly regulating key ribonucleic acid pathways and signaling pathways in cancer cells [58]. In addition, laboratory studies have indicated that propofol exerts anti-inflammatory and antioxidative effects [59-63], which may protect against perioperative immune suppression. The benefits observed for LRR could not be transferred to OS, possibly because of insufficient follow-up time and a relatively low reduction risk (hazard ratio =0.77, 95% CI= 0.58-0.87; **Table 3**). Future clinical studies should include a longer follow-up duration for women with breast IDC receiving BCS to examine benefits for OS.

Until now, no study has estimated the effect of DM on women with breast IDC receiving BCS under GA with or without propofol. To the best of our knowledge, this is the first study to show no DM benefits for patients with breast IDC receiving BCS under propofol-based TIVA-GA compared with non-propofol-based INHA-GA (**Table 4** and **Figure 1C**). Differentiated stage II and III [15, 18-21], pathologic stage III, pT2, pT3-4, pN1, pN2-3, and Her-2 positivity [64, 65] (**Table 4**) were determined as independent poor prognostic factors for DM; this finding is compatible with those of previous studies [15, 18-21]. Compared with no adjuvant chemotherapy, adjuvant chemotherapy was a more favorable independent prognostic factor for women with breast IDC receiving BCS, irrespective of whether they received propofol-based TIVA-GA or non-propofol-based INHA-GA. In our population, adjuvant chemotherapy was indicated for patients with breast cancer receiving BCS with risk factors following NCCN guidelines [30]. Adjuvant chemotherapy could reduce the risk of DM in women with breast IDC receiving BCS; this finding is in accordance with those of previous studies [64, 65]. In a preclinical study examining the effects of anesthetics on natural killer (NK) cell activity and metastasis in a rat model of breast cancer, propofol did not suppress NK cell activity or increase metastasis, whereas halothane, ketamine, and thiopental did [66]. However, no direct effect or clear pathway of the inhibition of cancer metastasis through anesthetic agents have been reported in previous studies, although some in vitro studies of breast cancer cell lines have indicated that propofol reduced the expression of neuroepithelial cell transforming gene 1, which promotes the migration of adenocarcinoma in vitro and increases cell apoptosis through the miR-24/p27 pathway [66-68]. In addition, in the present study, adjuvant chemotherapy might have masked the protective effects of propofol on the risk of DM because adjuvant chemotherapy reduces the risk of DM [64, 65]. Our clinical data indicated that propofol might not be associated with the risk of DM in patients with breast IDC receiving BCS.

The strength of this study is that it is the first and largest cohort study to estimate oncologic outcomes (OS, LRR, and DM) in patients with breast IDC receiving BCS under propofol-based TIVA-GA and non-propofol-based INHA-GA. Covariates between the two anesthesia techniques were homogenous for women with breast IDC receiving BCS, and no selection bias was noted for the two anesthesia techniques (**Table 1**). No study has estimated the effect of propofol-based TIVA-GA on oncologic outcomes (all-cause mortality, LRR, and DM) in patients with breast cancer receiving BCS and all prognostic factors including stages. In our study, poor differentiation, advanced pathologic stages, HR negativity, and HER-2 positivity were determined as poor prognostic factors for OS, LRR, and DM in patients with breast cancer receiving BCS (**Tables 2**-**4**); this finding is compatible with those of previous studies [15, 18-21]. Adjuvant RT could reduce the risk of LRR, whereas adjuvant chemotherapy could reduce the risk of DM in patients with breast IDC receiving BCS. However, propofol-based TIVA-GA in patients with breast IDC receiving BCS was only beneficial in reducing LRR and did not affect all-cause mortality or DM. This is the first study to show that propofol-based TIVA-GA reduced the risk of LRR. Previous studies did not

differentiate between recurrence, LRR, and DM [13-21, 55]. The findings should be considered in future clinical practice and prospective clinical trials.

This study has some limitations. First, because all patients with breast IDC were enrolled from an Asian population, the results may not be applicable to non-Asian populations; hence, our results should be cautiously extrapolated to non-Asian populations. However, no evidence is available to demonstrate differences in oncologic outcomes between Asian and non-Asian patients with breast IDC receiving BCS. Second, the diagnoses of all comorbid conditions were based on ICD-9-CM codes. Nevertheless, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of diagnoses, and hospitals with outlying charges or practices may be audited and heavily penalized if malpractice or discrepancies are identified. Accordingly, to obtain crucial information regarding population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. Finally, the TCRD does not contain information regarding dietary habits, socioeconomic status, or body mass index, all of which may be risk factors for mortality. However, considering the magnitude and statistical significance of observed effects in this study, these limitations are unlikely to affect conclusions.

Conclusions

Propofol-based TIVA-GA might be beneficial for reducing LRR in women with breast IDC receiving BCS compared with non-propofol-based INHA-GA. No association of the risk of OS or DM with propofol-based TIVA-GA or non-propofol-based INHA-GA was observed in patients with breast IDC receiving BCS.

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Disclosure of conflict of interest

None.

Abbreviations

OS, overall survival; LRR, locoregional recurrence; DM, distant metastasis; IDC, intraductal carcinoma; BCS, breast conserving surgery; TIVA, total intravenous anesthesia; GA, general anesthesia; INHA, inhalational; HR, hormone receptor; CI, confidence interval; RCT, randomized controlled trial; PSM, propensity score matching; TCRD, Taiwan Cancer Registry Database; SD, standard deviation; AJCC, American Joint Committee on Cancer; Her-2, human epidermal growth factor receptor-2; RT, radiotherapy; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification; pT, pathologic tumor stage; pN, pathologic nodal stage; NCCN, National Comprehensive Cancer Network.

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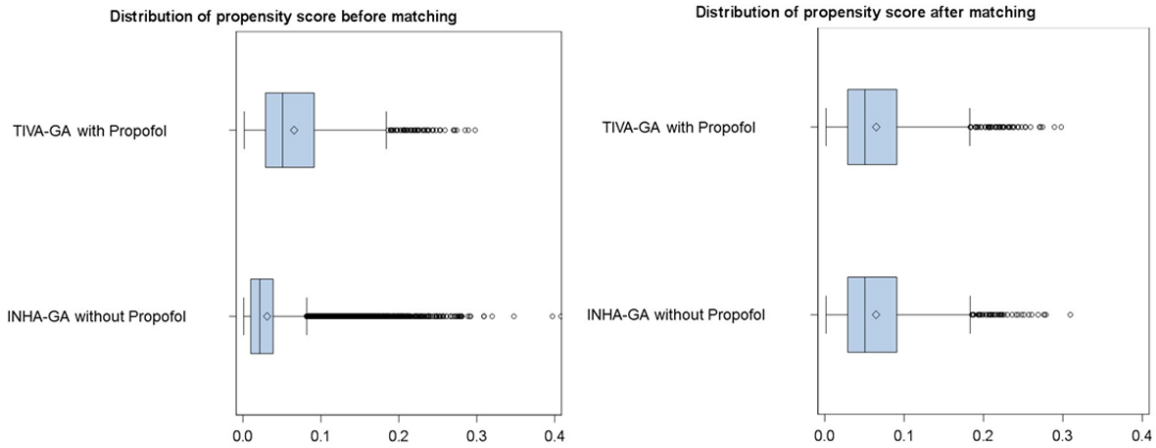
Supplementary Table 1. Demographics of patients with breast cancer receiving breast conserving surgery undergoing TIVA-GA with propofol or INHA-GA without propofol (Before propensity score-matched)

		TIVA-GA with Propofol N=1948	INHA-GA without Propofol N=58677	*P*-value
		n (%)	n (%)	
Age	Mean (SD)	54.7 (11.8)	54.2 (11.8)	0.0225*
	Median (Q1-Q3)	54 (46-63)	53 (46-62)	
	20-49	693 (35.6)	22240 (37.9)	0.0372#
	50+	1255 (64.4)	36437 (62.1)	
Diagnosis year	2009-2013	301 (15.5)	29342 (50.0)	<0.0001#
	2014-2018	1647 (84.5)	29335 (50.0)	
Menopausal status	Premenopausal	696 (35.7)	25201 (42.9)	<0.0001#
	Postmenopausal	1252 (64.3)	33476 (57.1)	
CCI Scores	0	1268 (65.1)	41864 (71.3)	<0.0001#
	1	410 (21.0)	11061 (18.9)	
	2+	270 (13.9)	5752 (9.8)	
Differentiation	I	389 (20.0)	8829 (15.0)	<0.0001#
	II	997 (51.2)	31790 (54.2)	
	III	562 (28.9)	18058 (30.8)	
AJCC Pathologic stage	I	774 (39.7)	21730 (37.0)	0.1801#
	II	867 (44.5)	30508 (52.0)	
	III	307 (15.8)	6439 (11.0)	
pT	pT1	917 (47.1)	28828 (49.1)	0.1120#
	pT2	892 (45.8)	25467 (43.4)	
	pT3-4	139 (7.1)	4382 (7.5)	
pN	pN0	1267 (65.0)	35412 (60.4)	0.0001#
	pN1	417 (21.4)	13966 (23.8)	
	pN2-3	264 (13.6)	9299 (15.8)	
ASA physical status	ASA I	1092 (56.1)	34785 (59.3)	0.0124#
	ASA II	454 (23.3)	12998 (22.2)	
	ASA III-IV	402 (20.6)	10894 (18.6)	
Adjuvant chemotherapy	No	702 (36.0)	20346 (34.7)	0.2140#
	Yes	1246 (64.0)	38331 (65.3)	
Adjuvant RT	No	190 (9.8)	4972 (8.5)	0.8824#
	Yes	1758 (90.2)	53705 (91.5)	
Hormone Receptor	No	965 (49.5)	23246 (39.6)	<0.0001#
	Yes	983 (50.5)	35431 (60.4)	
Her-2 receptor	No	1698 (87.2)	50364 (85.8)	0.0963#
	Yes	250 (12.8)	8313 (14.2)	
Nodal surgery	ALND	629 (32.3)	26989 (46.0)	<0.0001#
	SLNB	1319 (67.7)	31688 (54.0)	
Hospital level	Academic center	1631 (83.7)	34497 (58.8)	<0.0001#
	Nonacademic center	317 (16.3)	24180 (41.2)	
Follow-up time, months	Mean (SD)	63.3 (29.7)	62.2 (31.1)	
Death		143 (7.3)	7216 (12.3)	<0.0001#
Locoregional recurrence		88 (4.5)	4899 (8.3)	<0.0001#
Distant metastasis		177 (9.1)	8823 (15.0)	<0.0001#

IQR, interquartile range; TIVA, total intravenous anesthesia; GA, general anesthesia; INHA, inhalational; SD, standard deviation; AJCC, American Joint Committee on Cancer; Her-2, Human Epidermal Growth Factor Receptor-2; RT, radiotherapy; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; pT, pathologic tumor stage; pN, pathologic nodal stage; ALND, axillary lymph node dissection; SNLB, sentinel lymph node biopsy. #*P* value was estimated using the chi-square test; **P* value was estimated using independent t-test.



Supplementary Figure 1. Distribution of propensity score before and after matching.