ANESTHESIOLOGY

Total Intravenous Anesthesia *versus* Inhalation Anesthesia for Breast Cancer Surgery

A Retrospective Cohort Study

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ABSTRACT

Background: The association between type of anesthesia used and recurrence of cancer remains controversial. This retrospective cohort study compared the influence of total IV anesthesia and inhalation anesthesia on the primary outcome of recurrence-free survival after breast cancer surgery.

Methods: The authors reviewed the electronic medical records of patients who had breast cancer surgery at a tertiary care teaching hospital between January 2005 and December 2013. The patients were grouped according to whether IV or inhalation anesthesia was used for surgery. Propensity score matching was used to account for differences in baseline characteristics. Kaplan–Meier survival curves were constructed to evaluate the influence of type of anesthesia on recurrence-free survival and overall survival. The risks of cancer recurrence and all-cause mortality were compared between each type of anesthesia.

Results: Of 7,678 patients who had breast cancer surgery during the study period, data for 5,331 patients were available for analysis (IV group, n = 3,085; inhalation group, n = 2,246). After propensity score matching, 1,766 patients remained in each group. Kaplan–Meier survival curves showed that there was no significant difference in recurrence-free survival or overall survival between the two groups, with 5-yr recurrence-free survival rates of 93.2% (95% CI, 91.9 to 94.5) in the IV group and 93.8% (95% CI, 92.6 to 95.1) in the inhalation group. Inhalation anesthesia had no significant impact on recurrence-free survival (hazard ratio, 0.96; 95% CI, 0.69 to 1.32; $P = 0.782$) or overall survival (hazard ratio, 0.96; 95% CI, 0.69 to 1.33, $P = 0.805$) when compared with total IV anesthesia.

Conclusions: The authors found no association between type of anesthesia used and the long-term prognosis of breast cancer. The results of this retrospective cohort study do not suggest specific selection of IV or inhalation anesthesia for breast cancer surgery.

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EDITOR'S PERSPECTIVE

What We Know about This Topic

- IV anesthesia may impair anticancer immunity less than volatile anesthesia and therefore reduce recurrence risk

What This Article Tells Us That Is New

- In a large propensity-matched retrospective cohort analysis, the authors compared total IV and volatile anesthesia for breast cancer surgery
- Recurrence hazard was similar with each approach
- Selection of IV or volatile anesthesia should be based on factors other than cancer recurrence

Disease recurrence after cancer surgery is a major fear for patients. Several factors affect the risk of recurrence, including residual cancer cells at the surgical margin, the characteristics of the cancer cells, and host immune function. Paradoxically, surgery itself may facilitate distant metastasis of circulating cancer cells by inducing an inflammatory response and immunosuppression.[1–3] Furthermore, anesthetic drugs can have an unfavorable effect on the immune system.[4,5] Both surgery and anesthesia suppress cell-mediated immunity and increase angiogenesis and can therefore promote proliferation and metastasis of cancer cells during the perioperative period.[6] Decreased levels of circulating antiinflammatory cytokines and change in the functioning of natural killer cells have been reported to be mechanisms by which anesthetic techniques can affect immune function.[7–10]

Anesthetic agents vary in their ability to induce immunomodulation and potentiation of tumorigenic growth factors, including hypoxia-inducible factor-1 and insulin-like growth factor.[10–13] Several studies have reported that propofol has a more favorable immunomodulatory effect than inhalation agents.[8,9,14] Some clinical studies have shown that survival after cancer surgery is better in patients who receive total IV anesthesia than in those who receive inhalation anesthesia.[15–19] However, the data are presently inadequate, and more evidence is needed.

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Breast cancer is the most common type of malignancy in women. There has been some debate regarding the influence of anesthetic agents on the recurrence of breast cancer.[16,20] To address this controversy, we undertook a retrospective cohort study that included a large number of patients and was adjusted for strong prognostic factors, such as subtype of breast cancer and the chemotherapeutic modalities used. We hypothesized that there would be differences in recurrence-free survival and overall survival between patients who receive total IV anesthesia and those who receive inhalation anesthesia during breast cancer surgery. The primary purpose of this study was to assess the relationship between type of anesthesia and long-term outcomes after breast cancer surgery, using propensity score–matched analyses. The secondary purpose was to identify potential risk factors for cancer recurrence and all-cause mortality—including type of anesthesia—in patients with breast cancer, using multivariable Cox regression analyses.

Materials and Methods

The study was approved by the institutional review board of Seoul National University Hospital (approval number 1711-058-899). The requirement for informed consent was waived in view of the retrospective design of the study.

Study Population

We reviewed the electronic medical records of all patients who had breast cancer surgery at a tertiary care teaching hospital between January 2005 and December 2013. The exclusion criteria were as follows: bilateral breast cancer, immediate breast reconstruction surgery, metastatic breast cancer, other malignancy, history of breast surgery, administration of both IV and inhalation anesthetics, male sex, benign breast tumor or carcinoma *in situ*, American Society of Anesthesiologists (ASA) physical status greater than or equal to IV, and unknown type of anesthesia.

Patients were grouped according to whether they received total IV anesthesia (IV group) or inhalation anesthesia (inhalation group) for breast cancer surgery. The type of anesthesia was determined according to the preference of the attending anesthesiologists. Patients in the IV group received continuous administration of propofol and remifentanil *via* a target-controlled infusion pump, and those in the inhalation group received a volatile anesthetic agent (enflurane, isoflurane, sevoflurane, or desflurane). Those who received the same type of anesthesia for multiple surgeries during the study period remained eligible. None of the patients received additional regional anesthesia for postoperative pain control.

Variables and Outcome Measurements

We recorded the following data from the electronic medical records: age, height, weight, ASA physical status, date of surgery, anesthetic time, type of surgery (breast-conserving surgery or total mastectomy), perioperative use of opioids, use of ketorolac for postoperative analgesia, transfusion, tumor size, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 expression, Ki-67 expression, and whether postoperative adjuvant chemotherapy, radiation therapy, or hormone therapy was used. Based on estrogen receptor and progesterone receptor status and levels of human epidermal growth factor receptor 2 and Ki-67 expression, we determined the subtype of breast cancer in each patient as luminal A, luminal B, human epidermal growth factor receptor 2–enriched, or basal.[21] We also identified whether each patient adhered to standard cancer therapy. Nonadherence to standard cancer therapy was defined as not receiving anticancer treatment, including adjuvant chemotherapy, radiation therapy, and hormone therapy, as recommended in the National Comprehensive Cancer Network guideline for each type of cancer.[22] However, time to administration of standard cancer therapy was not considered.

The primary endpoint of the study was recurrence-free survival, which was defined as the interval between the date of surgery and the date of recurrence of breast cancer or death. Recurrence of breast cancer was determined as locoregional or systemic, and confirmed by radiologic or histologic examination. The secondary endpoint was overall survival, defined as the interval from the date of surgery to the date of death. The dates of death were obtained from the Korean Ministry of the Interior and Safety, using the resident registration number for each patient. Follow-up was concluded on December 31, 2015; therefore, the duration of follow-up ranged from 2 to 11 yr. Patients who were lost to follow-up during the study period were censored at the date of last follow-up.

Statistical Analysis

The sample size was based on the available data from all patients who had breast cancer surgery at our institution from January 2005 to December 2013. No statistical power calculation was performed before the study.

The study results are presented as the number (percentage) for categorical variables and as the mean ± SD or median [interquartile range] for continuous variables, as appropriate. The normality of the data distribution was assessed using the normal quantile–quantile plot. The independent samples *t* test or Mann–Whitney *U* test were used to compare continuous variables and the chi-square test to compare categorical variables between groups.

Propensity score matching was used to reduce the potential confounding effect of each variable and the differences in baseline characteristics between the groups. The propensity score was defined as the probability of receiving inhalation anesthesia by logistic regression analysis. The variables used for matching were age, height, weight, ASA physical status, anesthetic time, postoperative use of ketorolac, transfusion, type of surgery, subtype of breast cancer, nonadherence to standard cancer therapy, and year of surgery. Perioperative use of opioids was excluded from the model because all patients in the IV group received an opioid (remifentanil) intraoperatively. We matched patients at a ratio of 1:1 using the nearest neighbor method with a caliper of 0.05 SD of the logit of the propensity score. The balance of the matched patients was assessed using the standardized mean difference for each contributor.

In the propensity-matched cohort, recurrence-free survival and overall survival were estimated for up to 11 yr using the Kaplan–Meier method, and the groups were compared using the log-rank test. Cox proportional hazards models were used to compare hazard ratios for the two groups and to identify risk factors for recurrence of cancer and all-cause mortality; potential risk factors included type of anesthesia, age, anesthetic time, ASA physical status, type of surgery, perioperative use of opioids, postoperative use of ketorolac, transfusion, subtype of breast cancer, nonadherence to standard cancer therapy, and year of surgery. All variables were adjusted in multivariable Cox regression analysis using the enter method to assess the association of type of anesthesia with long-term outcome after breast cancer surgery. Patients with missing data were excluded from the analysis. Proportional hazard assumptions for categorical variables were assessed using log-minus-log survival plots, and restricted cubic splines were used for continuous variables, such as age and anesthetic time.[23,24] The log hazard was not linear for age, so the patients were categorized into the following groups based on age: less than 40 yr, 40 to 50 yr, and greater than or equal to 50 yr.

We performed an additional analysis using a Cox regression with inverse probability of treatment weighting to adjust for the propensity score, which differs from the model-based adjustment because it can deal with the possibility that patients with better prognosis are assigned to a particular group.[25] Perioperative use of opioids and type of anesthesia were included in the weighted Cox proportional hazards model because use of opioids was not adjusted for in the aforementioned model used for calculation of the propensity score.

All analyses were performed using R software version 3.4.4 (R Foundation for Statistical Computing, Austria). We used the package "survival" for the Cox regression analysis and "MatchIt" for the propensity score matching. The inverse probability of treatment weighting was conducted by using "weights" argument in "coxph" function. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Of 7,678 patients who had breast cancer surgery between January 2005 and December 2013 at Seoul National University Hospital, 5,331 patients (IV group, n = 3,085; inhalation group, n = 2,246) were finally included in the analyses (fig. 1). The distribution of patients who received IV or inhalation anesthesia according to the year of surgery is shown in Figure 1 (Supplemental Digital Content 1, http://links.lww.com/ALN/B807).

All patients in the IV group received propofol, and those in the inhalation group received sevoflurane (1,537 of 2,246; 68.4%), desflurane (700 of 2,246; 31.2%), enflurane (8 of 2,246; 0.35%), or isoflurane (1 of 2,246; 0.05%) for maintenance of general anesthesia. Table 1 shows the characteristics for the total study cohort and those for the propensity-matched cohort.

The median follow-up duration was 62 (interquartile range, 39 to 85) months for all patients, 67 (interquartile range, 48 to 86) months for the IV group, and 53 (interquartile range, 35 to 84) months for the inhalation group.

After propensity score matching, 1,766 patients remained in each group, with a good matching balance. All standardized mean differences for the study variables were less than 0.1 (table 1), and their distributions are shown in figure 2 (Supplemental Digital Content 1, http://links.lww.com/ALN/B807).

The Kaplan–Meier survival curves demonstrated 5-yr recurrence-free survival rates of 93.2% (95% CI, 91.9 to 94.5) in the IV group and 93.8% (95% CI, 92.6 to 95.1) in the inhalation group and respective 5-yr overall survival rates of 94.2% (95% CI, 92.9 to 95.5) and 94.5% (95% CI, 93.3 to 95.8). There was no significant difference in recurrence-free survival ($P = 0.491$) or overall survival ($P = 0.365$) between the IV group and the inhalation group in the propensity-matched cohort (fig. 2).

In the propensity-matched cohort, the Cox proportional hazards model for recurrence-free survival was constructed to evaluate the association between type of anesthesia and recurrence-free survival, the primary outcome of this study, and is shown in table 2. Multivariable Cox regression revealed no significant association between inhalation anesthesia and poorer recurrence-free survival (hazard ratio, 0.96; 95% CI, 0.69 to 1.32; $P = 0.782$; table 2) when compared with the IV anesthesia group.

Table 3 shows the Cox proportional hazards model for overall survival after breast cancer surgery in the propensity-matched cohort. After adjustment, inhalation anesthesia was not associated with a difference in

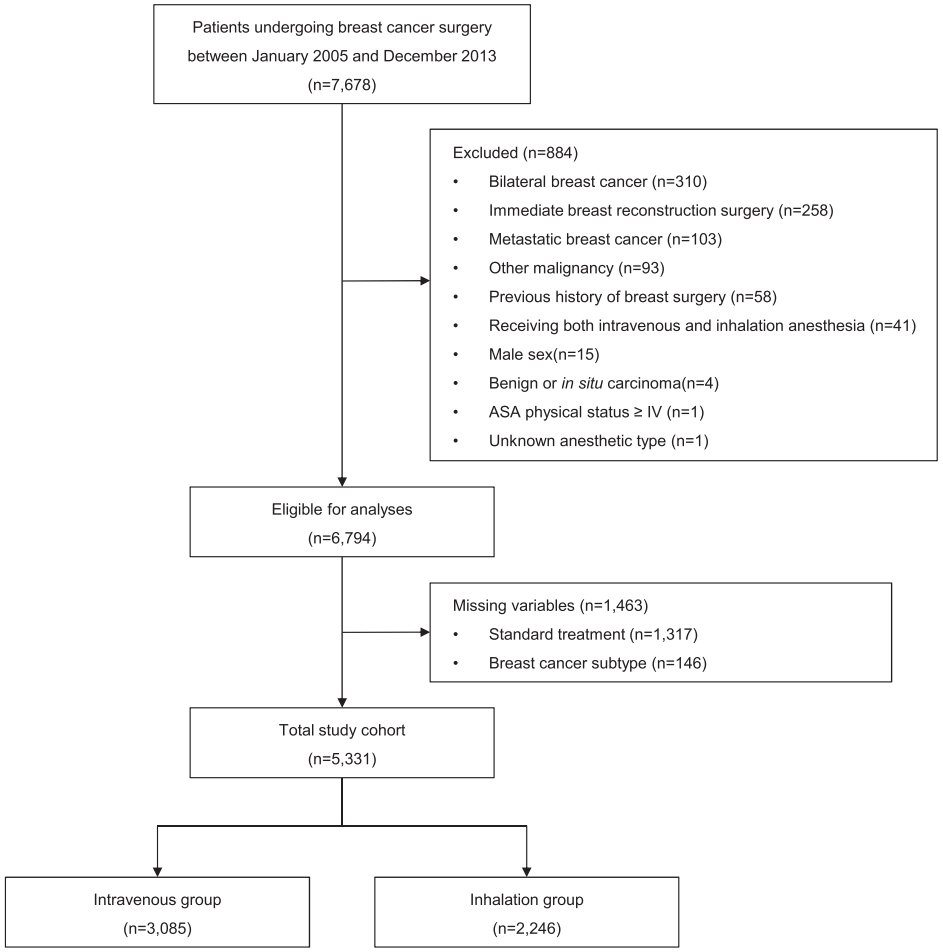

Fig. 1. Flow diagram of the study population. ASA, American Society of Anesthesiologists.

overall survival (hazard ratio, 0.96; 95% CI, 0.69 to 1.33, $P = 0.805$; table 3).

We also conducted the Cox regression analyses for the total study cohort to determine risk factors for cancer recurrence and all-cause mortality, the secondary outcome of this study. Age younger than 40 yr, ASA physical status, total mastectomy, subtype of breast cancer other than luminal-A, and nonadherence to standard cancer therapy were found to be associated with higher risks of cancer recurrence and all-cause mortality. The Cox proportional hazards models for recurrence-free survival and overall survival in the total study cohort are tabulated in tables 1 and 2 (Supplemental Digital Content 1, http://links.lww.com/ALN/B807), respectively.

The Cox regression analysis with inverse probability of treatment weighting also demonstrated that there was no significant association between type of anesthesia and recurrence-free survival (hazard ratio, 0.86; 95% CI, 0.65 to 1.14; $P = 0.293$) or overall survival (hazard ratio, 0.79; 95% CI, 0.59 to 1.04; $P = 0.091$).

Discussion

In this study, there was no influence of total IV anesthesia or inhalation anesthesia on recurrence-free survival or overall survival in patients who had breast cancer surgery. We found no significant association between type of anesthesia used and the prognosis after breast cancer surgery.

Numerous studies have investigated the influence of anesthetic technique on the prognosis in patients with cancer. Use of regional analgesia, including epidural and paravertebral block, was reported to be effective in reducing inflammation and preventing immunosuppression in patients undergoing cancer surgery.[26] Epidural analgesia for postoperative pain was found to be associated with an improved prognosis in patients with colon,[27] prostate,[28] rectal,[29] and gastric cancer.[30] Paravertebral analgesia was also reported to have a beneficial effect on the risk of recurrence of breast cancer.[31] In contrast, other studies reported that epidural analgesia did not have any clear impact on oncologic outcomes, such as disease recurrence,

Table 1. Patient Characteristics for the Total Study Cohort and for the Propensity-matched Cohort

	Total Study Cohort			Propensity-matched Cohort			
	IV (n = 3,085)	Inhalation (n = 2,246)	*P* Value	IV (n = 1,766)	Inhalation (n = 1,766)	*P* Value	Standardized Mean Difference
Patient-related							
Age, yr	50 ± 10	50 ± 10	0.753	50 ± 10	50 ± 10	0.976	−0.001
Height, cm	157 ± 5	157 ± 5	0.712	157 ± 5	157 ± 5	0.860	−0.006
Weight, kg	57 ± 8	58 ± 8	0.078	57 ± 8	57 ± 8	0.853	0.006
Body mass index, kg/m^2	23 ± 3	23 ± 3	0.116	23 ± 3	23 ± 3	0.835	
ASA physical status			0.019			0.624	
I	2,125 (68.9)	1,610 (71.7)		1,244 (70.5)	1,243 (70.4)		−0.001
II	944 (30.6)	617 (27.5)		511 (28.9)	507 (28.7)		−0.005
III	16 (0.5)	19 (0.8)		11 (0.6)	16 (0.9)		0.031
Anesthesia-related							
Anesthetic time, min	100 [87–120]	110 [90–130]	< 0.001	100 [88–120]	106 [90–126]	< 0.001	0.073
Perioperative opioid administration	3,085 (100.0)	1,103 (49.1)	< 0.001	1,766 (100.0)	870 (49.3)	< 0.001	
Postoperative use of ketorolac	1,701 (55.1)	1,181 (52.6)	0.069	983 (55.7)	975 (54.2)	0.398	−0.030
Transfusion	57 (1.8)	33 (1.5)	0.342	25 (1.4)	29 (1.6)	0.681	0.019
Cancer and surgery-related							
Type of surgery			0.025			0.777	
Breast conserving surgery	1,989 (64.5)	1,515 (67.5)		1,157 (65.5)	1,166 (66.0)		
Total mastectomy	1,096 (35.5)	731 (32.5)		609 (34.5)	600 (34.0)		−0.011
Subtype			0.015			0.979	
Luminal A	1,514 (49.1)	1,164 (51.8)		921 (52.2)	912 (51.6)		
Luminal B	656 (21.3)	484 (21.6)		383 (21.7)	391 (22.1)		0.011
HER2 overexpression	386 (12.5)	220 (9.8)		172 (9.7)	176 (10.0)		0.008
Basal	529 (17.1)	378 (16.8)		290 (16.4)	287 (16.3)		−0.004
Nonadherence to standard cancer therapy	1,070 (34.7)	932 (41.5)	< 0.001	666 (37.7)	660 (37.4)	0.862	−0.007
Year of surgery			< 0.001			0.640	
2005–2007	758 (24.6)	621 (27.7)		620 (35.1)	594 (33.6)		−0.033
2008–2010	1,518 (49.2)	344 (15.3)		341 (19.3)	344 (19.5)		0.005
2011–2013	809 (26.2)	1,281 (57.0)		805 (45.6)	828 (46.9)		

The data are presented as mean ± SD, median [interquartile range], or number (percentage).

ASA, American Society of Anesthesiologists; HER2, human epidermal growth factor 2; IV, intravenous.

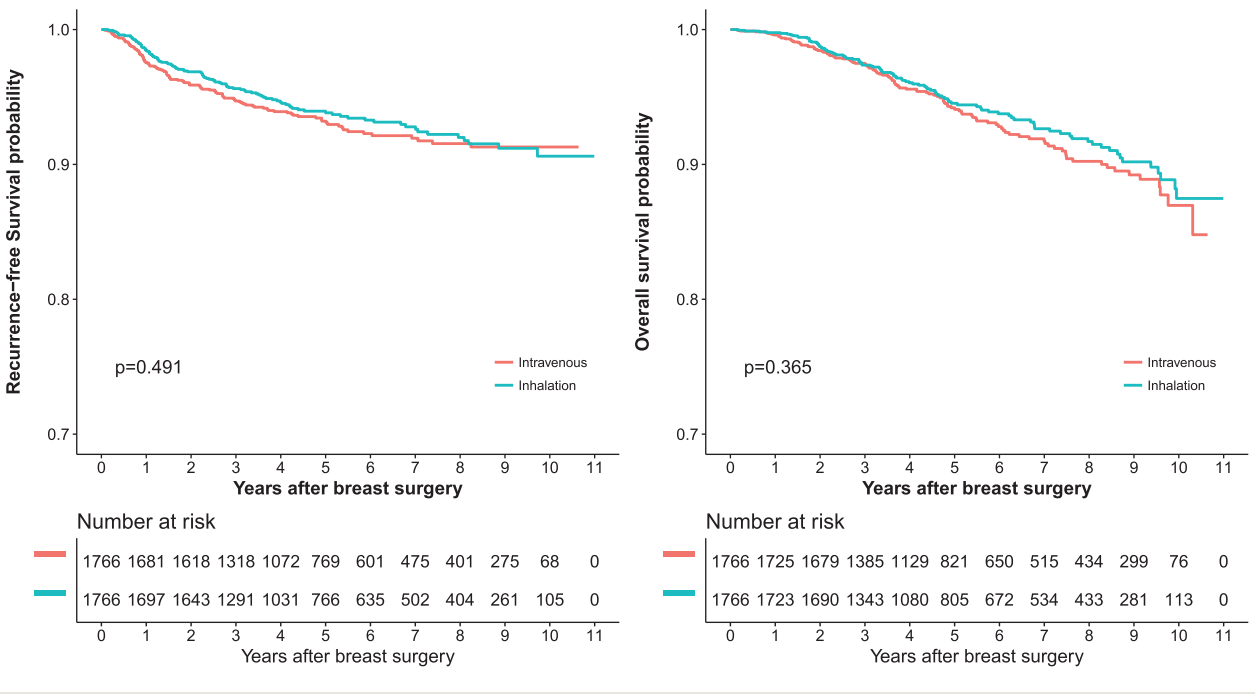

Fig. 2. Kaplan–Meier survival curve for recurrent-free survival and overall survival in propensity score-matched patients.

Table 2. Univariable and Multivariable Cox Regression Analysis for Recurrence-free Survival in the Propensity-matched Cohort

		Unadjusted			Adjusted		
	Recurrence/ Total No., %	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Type of anesthesia							
Total IV anesthesia	118/1,766 (6.7)	Reference			Reference		
Inhalation anesthesia	108/1,766 (6.1)	0.91	0.70–1.18	0.491	0.96	0.69–1.32	0.782
Age (yr)							
Age < 40	58/498 (11.6)	2.21	1.57–3.11	< 0.001	1.99	1.41–2.82	< 0.001
40 ≤ Age < 50	75/1,368 (5.5)	Reference			Reference		
Age ≥ 50	93/1,666 (5.6)	1.11	0.82–1.50	0.517	1.08	0.78–1.48	0.658
Anesthetic time (1 hr)		1.02	0.82–1.27	0.851	1.08	0.86–1.35	0.523
ASA physical status							
I	163/2,487 (6.6)	Reference					
II	62/1,018 (6.1)	1.01	0.75–1.35	0.957	1.18	0.87–1.61	0.289
III	1/27 (3.7)	0.62	0.09–4.44	0.636	0.52	0.07–3.91	0.524
Total mastectomy	99/1,209 (8.2)	1.44	1.11–1.88	0.006	1.08	0.82–1.43	0.561
Perioperative opioid administration	171/2,636 (6.5)	1.07	0.79–1.45	0.666	1.09	0.75–1.61	0.646
Postoperative use of ketorolac	141/1,940 (7.3)	1.34	1.02–1.76	0.032	1.19	0.91–1.57	0.204
Transfusion	5/54 (9.3)	1.59	0.66–3.86	0.305	1.52	0.61–3.82	0.372
Subtype							
Luminal A	63/1,833 (3.4)	Reference			Reference		
Luminal B	59/774 (7.6)	2.33	1.63–3.32	< 0.001	2.48	1.73–3.56	< 0.001
HER2 overexpression	46/348 (13.2)	4.37	2.99–6.39	< 0.001	5.38	3.62–8.00	< 0.001
Basal	58/577 (10.1)	3.17	2.22–4.52	< 0.001	3.37	2.35–4.83	< 0.001
Nonadherence to standard cancer therapy	69/1,326 (5.2)	0.95	0.71–1.27	0.722	2.30	1.64–3.23	< 0.001
Year of surgery							
2005–2007	143/1,214 (11.8)	2.89	2.05–4.08	< 0.001	4.60	3.07–6.89	< 0.001
2008–2010	37/685 (5.4)	1.45	0.94–2.25	0.093	1.67	1.06–2.64	0.026
2011–2013	46/1,633 (2.8)	Reference			Reference		

ASA, American Society of Anesthesiologists; HER2, human epidermal growth factor 2; IV, intravenous.

in patients with prostate cancer[32] or ovarian cancer.[33] Moreover, *post hoc* analysis of a prospective randomized controlled trial revealed no significant association between use of an epidural block and cancer-free survival,[34] and the same result was found in recent meta-analyses.[26,35]

Recently, the impact of the anesthetic agent used on the prognosis of various cancers has been evaluated. One study found that use of total IV anesthesia during surgery for esophageal cancer was associated with a better postoperative survival rate than inhalation anesthesia.[18] Another study that compared the 5-yr disease recurrence rate in patients with breast cancer who received propofol-based total IV anesthesia or sevoflurane-based inhalation anesthesia demonstrated that total IV anesthesia could reduce the risk of recurrence.[16] However, the statistical power of that study seemed to be low because of a small sample size. Another study reported no significant difference in cancer-free survival or overall survival according to the type of anesthesia used.[20] However, that study included only 56 patients in the IV group. Our present study included a larger population with similar numbers of patients in both groups to strengthen its statistical power. Furthermore, we obtained clinically relevant results by adjusting for subtype of breast cancer, which is determined based on the gene expression profile and known to be closely associated with the clinical prognosis of breast cancer.[21,36] The molecular subtypes of breast cancer have been incorporated into the latest edition of the American Joint Committee on Cancer staging system.[37] We also included details of whether each patient adhered to the standard cancer therapy recommended in the recent guideline of the National Comprehensive Cancer Network as a covariate in our regression analyses to adjust for the interaction between use of adjuvant chemotherapy or radiation therapy and tumor, node, and metastasis disease stage classification.

The mechanism through which anesthesia affects the prognosis of cancer is thought to be the immunomodulatory effect of anesthetic agents. Cell-mediated immunity plays an important role in preventing dissemination and implantation of cancer cells, which are facilitated by the stress response and tissue damage induced by surgery.[3,38] Both *in vitro* and *in vivo* studies have found that volatile anesthetic agents suppress the functioning of natural killer cells,[14,39,40] which is critical in preventing growth of cancer cells. In contrast,

Table 3. Univariable and Multivariable Cox Regression Analysis for Overall Survival in the Propensity-matched Cohort

		Unadjusted			Adjusted		
	Death/Total No., %	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Type of anesthesia							
Total IV anesthesia	116/1,766 (6.6)	Reference			Reference		
Inhalation anesthesia	103/1,766 (5.8)	0.88	0.68–1.15	0.366	0.96	0.69–1.33	0.805
Age, yr							
Age < 40	58/498 (11.6)	2.83	1.97–4.07	< 0.001	2.47	1.71–3.57	< 0.001
40 ≤ Age < 50	58/1,368 (4.2)	Reference			Reference		
Age ≥ 50	103/1,666 (6.2)	1.74	1.26–2.40	0.001	1.24	0.88–1.74	0.221
Anesthetic time (1 hr)		1.11	0.89–1.38	0.366	1.13	0.89–1.42	0.318
ASA physical status							
I	132/2,487 (5.3)	Reference			Reference		
II	79/1,018 (7.8)	1.72	1.30–2.27	< 0.001	1.78	1.32–2.39	< 0.001
III	8/27 (29.6)	6.96	3.41–14.22	< 0.001	6.27	2.86–13.74	< 0.001
Total mastectomy	112/1,209 (9.3)	1.78	1.37–2.32	< 0.001	1.51	1.14–2.00	0.004
Perioperative opioid administration	168/2,636 (6.4)	1.18	0.86–1.61	0.308	1.19	0.80–1.76	0.395
Postoperative use of ketorolac	130/1,940 (6.7)	1.16	0.88–1.52	0.283	1.13	0.86–1.49	0.385
Transfusion	3/54 (5.6)	1.04	0.33–3.24	0.950	0.42	0.12–1.44	0.168
Subtype							
Luminal A	55/1,833 (3.0)	Reference			Reference		
Luminal B	54/774 (7.0)	2.40	1.65–3.49	< 0.001	2.43	1.66–3.55	< 0.001
HER2 overexpression	36/348 (10.3)	3.96	2.60–6.04	< 0.001	4.47	2.89–6.91	< 0.001
Basal	74/577 (12.8)	4.76	3.36–6.76	< 0.001	5.18	3.63–7.38	< 0.001
Nonadherence to standard cancer therapy	72/1,326 (5.4)	1.59	1.18–2.14	0.002	2.14	1.51–3.03	< 0.001
Year of surgery							
2005–2007	132/1,214 (10.9)	0.91	0.64–1.29	0.600	1.34	0.89–2.03	0.160
2008–2010	25/685 (3.6)	0.45	0.28–0.72	0.001	0.49	0.30–0.81	0.005
2011–2013	62/1,633 (3.8)	Reference			Reference		

ASA, American Society of Anesthesiologists; HER2, human epidermal growth factor 2, IV, intravenous.

propofol, a widely used IV anesthetic agent, was found to preserve the activity of natural killer cells and to have a protective anticancer effect.[9] Furthermore, several studies have demonstrated that volatile anesthetic agents induce upregulation of tumorigenic growth factors, including hypoxia-inducible factor-1 and vascular endothelial growth factor.[11,41] Anesthesia-related immunomodulation has also been proposed as the mechanism by which regional anesthesia may improve survival in patients with cancer.[26] Although a number of studies suggest a favorable impact of regional anesthesia on the prognosis of cancer, the evidence for such a benefit remains inadequate.[26,42] Similarly, conflicting results have been reported with regard to the association between use of total IV anesthesia and a decrease in the risk of recurrence of cancer.[43,44] Any conclusions regarding this association must await the results of the prospective randomized controlled trials currently in progress around the world.

Opioids have also been suggested to promote proliferation and angiogenesis of cancer cells by inhibiting cell-mediated immunity.[45,46] In our study, all patients in the IV group had received remifentanil, but not those in the inhalation group, so there was a difference in opioid use between the two groups. However, given that we found no significant association between use of opioids and outcomes after breast cancer surgery, the clinical impact of perioperative opioid administration on the long-term prognosis does not seem to be significant. Indeed, a recent large prospective population-based cohort study reported that use of opioids was not associated with recurrence of breast cancer.[47]

Our study confirmed a strong association between the subtype of breast cancer and the risks of cancer recurrence and death. Nonadherence to standard cancer therapy was also found to be associated with worse outcomes after breast cancer surgery, as would be expected. However, several factors, including postoperative complications, multiple neoadjuvant chemotherapy, and comorbidities, can impede a patient's ability to complete the intended oncologic treatment and are independently associated with poor long-term oncologic outcomes.[48] Although there was a strong association between ASA physical status and overall mortality in this study, this parameter,

which reflects how frail a patient is, may also have had an impact on nonadherence to standard cancer therapy. Other studies have also identified poor ASA physical status to be an independent risk factor for decreased long-term survival in patients with cancer.[17,49] We determined all-cause mortality rather than cancer-related mortality as an outcome variable in this study, and it is obvious that patients with multiple complicated comorbidities have a higher mortality rate.

Several limitations should be considered when interpreting the results of this study. First, a number of patients were excluded because of missing variables relating to their gene expression profiles and use of adjuvant chemotherapy and radiation therapy that were necessary to determine the subtype of breast cancer and nonadherence to standard cancer therapy. These exclusions may have introduced a degree of selection bias. Second, we could not take into account the medical advances that took place during our relatively long study period; changes in insurance coverage for trastuzumab in particular may have confounded the results. Third, because we determined the sample size on the basis of the data available during the study period rather than by *a priori* calculation, we cannot exclude the possibility that the lack of statistical significance may have resulted from inadequate statistical power to detect a potential difference between the two groups. Fourth, the time lapse until administration of standard cancer therapy, such as trastuzumab, was not considered. Finally, because of the retrospective study design, it was not possible to measure levels of inflammatory biomarkers that could explain the causal relationship between type of anesthesia used and recurrence of cancer.

In conclusion, we found no significant impact of total IV anesthesia or inhalation anesthesia on recurrence of breast cancer and overall survival in patients with the disease. Both anesthetic techniques can be used for breast cancer surgery, and the choice of anesthetic agent should be made according to the characteristics of the individual patient.

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Competing Interests

The authors declare no competing interests.

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References

1. Lennard TW, Shenton BK, Borzotta A, Donnelly PK, White M, Gerrie LM, Proud G, Taylor RM: The influence of surgical operations on components of the human immune system. Br J Surg 1985; 72:771–6
2. Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, Naritake Y, Hosokawa T, Kajiwara T: Suppression of cellular immunity by surgical stress. Surgery 2000; 127:329–36
3. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK: Perioperative events influence cancer recurrence risk after surgery. Nat Rev Clin Oncol 2018; 15:205–18
4. Byrne K, Levins KJ, Buggy DJ: Can anesthetic–analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J Anaesth 2016; 63:184–92
5. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y: Immune modulation by volatile anesthetics. Anesthesiology 2016; 125:399–411
6. Kim R: Anesthetic technique and cancer recurrence in oncologic surgery: Unraveling the puzzle. Cancer Metastasis Rev 2017; 36:159–77
7. O'Riain SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC: Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. Anesth Analg 2005; 100:244–9
8. Ke JJ, Zhan J, Feng XB, Wu Y, Rao Y, Wang YL: A comparison of the effect of total intravenous anaesthesia with propofol and remifentanil and inhalational anaesthesia with isoflurane on the release of pro- and anti-inflammatory cytokines in patients undergoing open cholecystectomy. Anaesth Intensive Care 2008; 36:74–8
9. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S: Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: Mediating mechanisms and prophylactic measures. Anesth Analg 2003; 97:1331–9
10. Buckley A, McQuaid S, Johnson P, Buggy DJ: Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. Br J Anaesth 2014; 113:i56–62
11. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, Brown R, Ma D: Prostate cancer cell

malignancy *via* modulation of HIF-1α pathway with isoflurane and propofol alone and in combination. Br J Cancer 2014; 111:1338–49
12. Rohwer N, Lobitz S, Daskalow K, Jöns T, Vieth M, Schlag PM, Kemmner W, Wiedenmann B, Cramer T, Höcker M: HIF-1α determines the metastatic potential of gastric cancer cells. Br J Cancer 2009; 100:772–81
13. Luo X, Zhao H, Hennah L, Ning J, Liu J, Tu H, Ma D: Impact of isoflurane on malignant capability of ovarian cancer *in vitro*. Br J Anaesth 2015; 114:831–9
14. Dubowitz JA, Sloan EK, Riedel BJ: Implicating anaesthesia and the perioperative period in cancer recurrence and metastasis. Clin Exp Metastasis 2018; 35:347–58
15. Soltanizadeh S, Degett TH, Gögenur I: Outcomes of cancer surgery after inhalational and intravenous anesthesia: A systematic review. J Clin Anesth 2017; 42:19–25
16. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS: Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: A retrospective study. Korean J Anesthesiol 2016; 69:126–32
17. Wigmore TJ, Mohammed K, Jhanji S: Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery: A retrospective analysis. Anesthesiology 2016; 124:69–79
18. Jun IJ, Jo JY, Kim JI, Chin JH, Kim WJ, Kim HR, Lee EH, Choi IC: Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery: A retrospective observational study. Sci Rep 2017; 7:14020
19. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L: The choice of anaesthetic–sevoflurane or propofol–and outcome from cancer surgery: A retrospective analysis. Ups J Med Sci 2014; 119:251–61
20. Kim MH, Kim DW, Kim JH, Lee KY, Park S, Yoo YC: Does the type of anesthesia really affect the recurrence-free survival after breast cancer surgery? Oncotarget 2017; 8:90477–87
21. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, Shi B: Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res 2015; 5:2929–43
22. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz MP, Goldstein LJ, Isakoff SJ, Lyons J, Marcom PK, Mayer IA, McCormick B, Moran MS, O'Regan RM, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Sitapati A, Smith KL, Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R: NCCN guidelines insights: Breast cancer, version 1.2017. J Natl Compr Canc Netw 2017; 15:433–51
23. Govindarajulu US, Spiegelman D, Thurston SW, Ganguli B, Eisen EA: Comparing smoothing techniques in Cox models for exposure-response relationships. Stat Med 2007; 26:3735–52
24. Durrleman S, Simon R: Flexible regression models with cubic splines. Stat Med 1989; 8:551–61
25. Cole SR, Hernán MA: Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed 2004; 75:45–9
26. Pérez-González O, Cuéllar-Guzmán LF, Soliz J, Cata JP: Impact of regional anesthesia on recurrence, metastasis, and immune response in breast cancer surgery: A systematic review of the literature. Reg Anesth Pain Med 2017; 42:751–6
27. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE: Long-term survival after colon cancer surgery: A variation associated with choice of anesthesia. Anesth Analg 2008; 107:325–32
28. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ: Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: A retrospective analysis. Anesthesiology 2008; 109:180–7
29. Gupta A, Björnsson A, Fredriksson M, Hallböök O, Eintrei C: Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: A retrospective analysis of data from 655 patients in central Sweden. Br J Anaesth 2011; 107:164–70
30. Wang Y, Wang L, Chen H, Xu Y, Zheng X, Wang G: The effects of intra- and post-operative anaesthesia and analgesia choice on outcome after gastric cancer resection: A retrospective study. Oncotarget 2017; 8:62658–65
31. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI: Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105:660–4
32. Forget P, Tombal B, Scholtès JL, Nzimbala J, Meulders C, Legrand C, Van Cangh P, Cosyns JP, De Kock M: Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol 2011; 28:830–5
33. Capmas P, Billard V, Gouy S, Lhommé C, Pautier P, Morice P, Uzan C: Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. Anticancer Res 2012; 32:1537–42
34. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI; ANZCA Trials Group Investigators: Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: Randomised trial. BMJ 2011; 342:d1491
35. Liu ZQ, Chen XB, Li HB, Qiu MT, Duan T: A comparison of remifentanil parturient-controlled intravenous analgesia with epidural analgesia: A meta-analysis of randomized controlled trials. Anesth Analg 2014; 118:598–603
36. Kast K, Link T, Friedrich K, Petzold A, Niedostatek A, Schoffer O, Werner C, Klug SJ, Werner A, Gatzweiler A,

Richter B, Baretton G, Wimberger P: Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat 2015; 150:621–9
37. Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ, Guiliano A: Breast, AJCC Cancer Staging Manual, 8th edition. Edited by Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. New York, Springer International Publishing, 2016
38. Gottschalk A, Sharma S, Ford J, Durieux ME, Tiouririne M: The role of the perioperative period in recurrence after cancer surgery. Anesth Analg 2010; 110:1636–43
39. Woo JH, Baik HJ, Kim CH, Chung RK, Kim DY, Lee GY, Chun EH: Effect of propofol and desflurane on immune cell populations in breast cancer patients: A randomized trial. J Korean Med Sci 2015; 30:1503–8
40. Miyata T, Kodama T, Honma R, Nezu Y, Harada Y, Yogo T, Hara Y, Tagawa M: Influence of general anesthesia with isoflurane following propofol-induction on natural killer cell cytotoxic activities of peripheral blood lymphocytes in dogs. J Vet Med Sci 2013; 75:917–21
41. Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, Takata M, Ma D: Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential *via* the hypoxia-inducible factor cellular signaling pathway *in vitro*. Anesthesiology 2013; 119:593–605
42. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL: Anaesthetic techniques for risk of malignant tumour recurrence. Cochrane Database Syst Rev 2014:CD008877
43. Owusu-Agyemang P, Cata JP, Fournier KF, Zavala AM, Soliz J, Hernandez M, Hayes-Jordan A, Gottumukkala V: Evaluating the impact of total intravenous anesthesia on the clinical outcomes and perioperative NLR and PLR profiles of patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2016; 23:2419–29
44. Margarit SC, Vasian HN, Balla E, Vesa S, Ionescu DC: The influence of total intravenous anaesthesia and isoflurane anaesthesia on plasma interleukin-6 and interleukin-10 concentrations after colorectal surgery for cancer: A randomised controlled trial. Eur J Anaesthesiol 2014; 31:678–84
45. Gach K, Wyrębska A, Fichna J, Janecka A: The role of morphine in regulation of cancer cell growth. Naunyn Schmiedebergs Arch Pharmacol 2011; 384:221–30
46. Singleton PA, Moss J: Effect of perioperative opioids on cancer recurrence: A hypothesis. Future Oncol 2010; 6:1237–42
47. Cronin-Fenton DP, Heide-Jørgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlertsen B, Sjøgren P, Kehlet H, Sørensen HT: Opioids and breast cancer recurrence: A Danish population-based cohort study. Cancer 2015; 121:3507–14
48. Aloia TA, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey JN: Return to intended oncologic treatment (RIOT): A novel metric for evaluating the quality of oncosurgical therapy for malignancy. J Surg Oncol 2014; 110:107–14
49. Cao L, Chang Y, Lin W, Zhou J, Tan H, Yuan Y, Zeng W: Long-term survival after resection of hepatocellular carcinoma: A potential risk associated with the choice of postoperative analgesia. Anesth Analg 2014; 118:1309–16