Long-term Survival for Patients Undergoing Volatile *versus* IV Anesthesia for Cancer Surgery

A Retrospective Analysis

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ABSTRACT

Background: Surgical resection remains the best option for long-term survival in many solid tumors. Surgery can, however, lead to tumor cell release into the circulation. Data have suggested differential effects of anesthetic agents on cancer cell growth. This retrospective analysis investigated the association of anesthetic technique with long-term survival in patients presenting for elective surgery in a comprehensive cancer center over 3 yr.

Methods: All patients undergoing elective surgery between June 2010 and May 2013 were included. Patients were grouped according to whether they had received volatile inhalational (INHA) or total IV anesthesia (TIVA). After excluding those who received both forms of anesthesia during the study period, Kaplan–Meier survival curves were constructed from the date of surgery to death. After propensity matching, univariate and multivariable regression models were used to compare hazard ratios for death.

Results: A total of 11,395 anesthetics using INHA or TIVA were delivered in the study period. After exclusions, 3,316 patients (796 deaths, 24%) remained in the INHA group and 3,714 (504 deaths, 13.5%) in the TIVA group. After propensity matching, 2,607 patients remained in each group (597 deaths, 22.8%, in INHA group *vs.* 407, 15.6%, in TIVA group). Volatile inhalational anesthesia was associated with a hazard ratio of 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariable analysis of known confounders in the matched group.

Conclusions: This retrospective analysis demonstrates an association between type of anesthetic delivered and survival. This analysis alongside biological plausibility should lead to urgent prospective work exploring the effect of anesthetic technique on survival. **(Anesthesiology 2016; 124:00-00)**

THERE were an estimated 14.1 million new cases of cancer worldwide in 2012, and this is expected to increase to 21.7 million by 2030.[1] Although the proportion of patients undergoing subsequent surgical resection varies from approximately 5 to 80% according to tumor type,[2] surgical resection remains the best chance of long-term survival for many solid cancers. Paradoxically, there is some evidence that surgery itself may be associated with tumor proliferation or metastasis.[3] Surgical excision can disrupt the tumor and/or the blood vessels supplying it, leading to the dissemination of tumor cells into the peripheral circulation.[4,5] The presence of circulating tumor cells has been associated with worse long-term outcomes.[6,7] Surgical stress leads to metabolic and neuroendocrine changes causing significant depression of cell-mediated immunity, which may otherwise prevent the implantation of circulating tumor cells.[8] This combination of potential tumor seeding and an impaired immune response makes patients undergoing cancer surgery susceptible to the development of metastasis. This has led to increasing interest in the perioperative period and its impact on cancer progression.

What We Already Know about This Topic

- General anesthetic drugs may influence host defenses against cancer

What This Article Tells Us That Is New

- In a retrospective analysis, the authors compared mortality after cancer surgery in more than 7,000 patients given volatile general anesthesia or total IV anesthesia
- Mortality was approximately 50% greater with volatile than with IV anesthesia, with an adjusted hazard ratio of 1.46 (1.29 to 1.66)

There are a number of retrospective studies suggesting benefit from the use of regional anesthesia during cancer

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Dr. Wigmore did all the initial data extraction and analysis and wrote the results and discussion section of the initial draft; Dr. Jhanji contributed to analysis, wrote the introduction, and revised the discussion and results; and Mr. Mohammed undertook all formal statistical analyses.

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surgery.[9,10] The reason for this benefit is unclear, but it may be due to the avoidance of opioids that have been implicated in potentiating tumor cell survival and angiogenesis.[11] More recent data have suggested variable effects of different general anesthetic agents on cancer cell growth *via* both immunomodulation[12,13] and the potentiation of tumorigenic growth factors including hypoxia-inducible factors (HIFs) and insulin-like growth factor (IGF).[14,15] HIFs are ubiquitous in humans and govern the response to hypoxia including angiogenesis and cell proliferation. Alongside normal cells, cancer cells also rely on these factors for their survival. An association between high levels of HIF and poor prognosis has been demonstrated by clinical studies in a number of solid cancers.[16,17] Similarly, overexpression of IGFs has been noted in many cancers and contributes to progression of cell cycle and inhibition of cellular apoptosis.[18]

There are two main classes of drugs used to maintain general anesthesia. The most commonly used are volatile inhalational anesthetic gases. These are halogen-containing hydrocarbons and are used for more than 90% of general anesthetics in the United Kingdom.[19] The main alternative is propofol, which is administered as an IV infusion (usually in combination with an opioid infusion). A number of studies have demonstrated both deleterious effects on the function of natural killer cells[12,13] and up-regulation of HIF[14] associated with the administration of volatile inhalational anesthetic agents and enhanced angiogenesis.[20] In addition, recent work has also suggested that volatile inhalational agents may increase IGF.[15] In contrast, there are data suggesting a reduction in the expression of HIF-1α by propofol.[14] This leads to the suggestion that the use of volatile inhalational agent in anesthesia may augment cancer cell growth with the alternative (propofol) having a converse (beneficial) effect.

Within the United Kingdom, less than 10% of general anesthetics delivered use propofol in preference to volatile inhalational agents for maintaining anesthesia due to increased drug and equipment costs and to a lack of familiarity with the IV technique.[19] Our institution is unusual in that there is close to an even split between the two, with the ultimate choice being dependant on an individual consultant's preference. We hypothesized that those patients receiving the volatile option might have a subsequent worse outcome. Therefore, we undertook a retrospective review of the association of anesthetic technique (volatile inhalational [INHA] *vs.* total IV anesthesia [TIVA] using propofol and a short-acting opioid, remifentanil) with long-term survival in patients presenting for elective surgery in our comprehensive cancer center during a 3-yr period.

Materials and Methods

Study Design

This was a retrospective cohort study.

Setting

The study was conducted at the Royal Marsden Foundation Trust, London, United Kingdom, a tertiary comprehensive cancer center.

Participants

All patients presenting for elective surgery over a 3-yr period (June 2010 to May 2013) who required general anesthesia were included. Patients were divided into those who received volatile inhalational (INHA) anesthesia and those who received TIVA. Patients in the TIVA group received continuous infusions of propofol and remifentanil. Patients in the volatile inhalational anesthesia group received a volatile inhalational agent (sevoflurane or isoflurane) and supplementary opioid at the discretion of the anesthetist. No patients received nitrous oxide. Type of anesthesia was according to the anesthetist preference. Patients were excluded if they received both forms of anesthesia within the study period, either during the same surgical procedure or for additional procedures. Patients who had multiple procedures during the study period and received the same form of anesthesia remained eligible.

Variables

Patient data retrospectively collected included anesthetic technique, age at the time of surgery, sex, severity of surgery, procedure, tumor site and group, the presence of distant metastasis at the time of surgery, intraoperative blood transfusion, the use of epidural analgesia, height and weight (where available), and use of opioids. Use of opioids was subsequently not included in the analysis as all but six cases received them. Preoperative morbidity was assessed by the I (least morbidity) to V (highest) American Society of Anesthesiologists (ASA) rating scale as recorded by the anesthetist or the preassessment team preoperatively. Surgical severity was graded from 1 (least) to 4 (most) according to a scale derived by the National Institute for Health and Care Excellence in their guidance for the use of preoperative tests for routine surgery.[21] When patients underwent multiple surgeries in the study period, that with the highest severity index was chosen. When surgeries had the same severity index, the first was chosen. These variables were chosen as potential confounders as they have either been shown, or posited, to affect outcome. Patients were followed-up only against the primary outcome, that is, survival.

Data Sources/Measurement

All data related to the procedure and anesthetic were obtained from the hospital theater care record (Intellivue Care Information Portfolio; Philips, The Netherlands). Data relating to the tumor type and presence of metastasis were obtained from the hospital electronic patient record. Data relating to deaths were obtained by submitting a batch data request to the NHS Personal Demographics Services.

Study Size

The study sample size was chosen as all patients older than 16 yr presenting for elective procedures between June 2010 and May 2013. All available patients were considered, and no *a priori* power analysis was conducted.

Statistical Methods

Patient demographics, disease stage, and surgery data were compared in the groups using chi-square and *t* tests as appropriate. The Kaplan–Meier method was used to calculate the overall survival of patients from the date of surgery to the date of death; patients alive were censored at the follow-up closure date (October 31, 2014). A Cox proportional hazard regression model was used to compare the hazard of the two groups by using a univariate model. A multivariable model was used to adjust for significant variables from the univariate models. A two-sided 5% α level was used to assess statistically significant difference in the models. All variables were forced into the multivariable models using enter method, which was used to fit the multivariable model (IBM SPSS version 22.0; IBM Inc., USA). All variables included in the multivariable model have complete data. The same Cox proportional hazard regression model was used to investigate the interaction between different types of anesthesia and individually ASA, metastases, and severity. Subgroup analyses were performed for cancer diagnosis (as different cancers have a different initial prognosis) and surgical severity (as it was felt *a priori* to potentially have an impact on outcome). Subgroup analyses were also performed for metastasis and ASA because each had a significant interaction with type of anesthesia. To account for differences in baseline characteristics, propensity scores were obtained by using binary logistic regression using all the patients' demographics presented in table 1. Matching

Table 1. Patient Demographics, Disease Stage, and Surgery Types for Overall Group and Matched Group after Propensity Scoring

	Overall Patients			Matched Patients		
	INHA	TIVA	*P* Value	INHA	TIVA	*P* Value
Variables	(n = 3,316)	(n = 3,714)		(n = 2,607)	(n = 2,607)	
Age (yr)						
Mean (SD)	57 (15.2)	57 (14.4)	0.256*	57 (15.1)	57 (14.9)	0.332†
BMI	2,741	3,175	0.257*	2,145	2,257	0.192
Mean (SD)	27 (5.7)	27 (5.1)		27 (5.6)	27 (5.2)	
	n (%)	n (%)		n (%)	n (%)	
Sex						
Male	1,415 (43)	1,181 (32)	< 0.001	991 (38)	995 (38)	0.909
Female	1,901 (57)	2,533 (68)		1,616 (62)	1,612 (62)	
Blood transfusion						
No	3,058 (92)	3,586 (97)	< 0.001	2,457 (94)	2,497 (96)	0.011
Yes	258 (8)	128 (3)		150 (6)	110 (4)	
Epidural use						
No	2,922 (88)	3,392 (91)	< 0.001	2,311 (89)	2,320 (88)	0.692
Yes	394 (12)	322 (9)		296 (11)	287 (11)	
ASA						
I	427 (13)	727 (20)	< 0.001	391 (15)	382 (15)	0.876
II	2,041 (62)	2,376 (64)		1,663 (64)	1,670 (64)	
III	827 (25)	597 (16)		536 (20)	542 (21)	
IV	21 (0.6)	14 (0.4)		17 (1)	13 (1)	
Surgical severity group						
1	377 (11)	254 (7)	< 0.001	212 (8)	235 (9)	0.430
2	1,424 (43)	2,244 (60)		1,323 (51)	1,302 (50)	
3	767 (23)	722 (19)		600 (23)	626 (24)	
4	748 (23)	494 (13)		472 (18)	444 (17)	
Metastases at surgery						
No	2,474 (75)	2,998 (81)	< 0.001	1,986 (76)	2,009 (77)	0.452
Yes	842 (25)	716 (19)		621 (24)	598 (23)	
BMI	n = 2,741	n = 3,175	0.001	n = 1,858	n = 1,858	0.241†
Underweight (< 18.5)	72 (3)	45 (1)		48 (2)	34 (1)	
Normal (18.5–24.9)	1,064 (39)	1,153 (36)		843 (39)	811 (36)	
Overweight (25.0–29.9)	962 (35)	1,209 (38)		759 (35)	868 (39)	
Obesity (≥ 30)	643 (23)	768 (24)		495 (23)	544 (24)	

* Independent *t* test, † paired *t* test.

ASA = American Society of Anesthesiologists; BMI = body mass index; INHA = volatile inhalational; TIVA = total IV anesthesia.

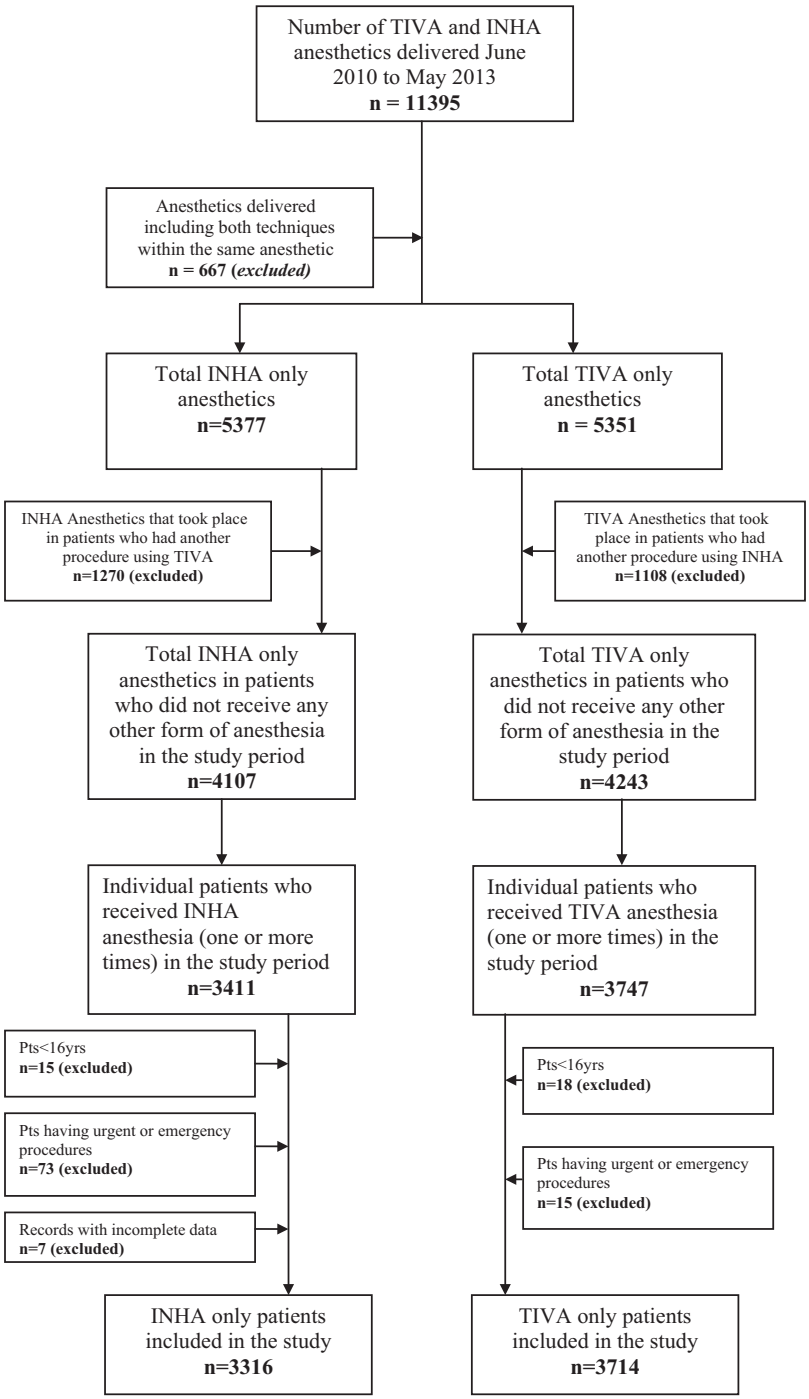

Fig. 1. Flow diagram detailing the selection of patients included in the retrospective analysis. Patients were excluded if they received both forms of anesthesia within the study period, either during the same surgical procedure or for additional procedures. Patients who had multiple procedures during the study period and received the same form of anesthesia remained eligible. INHA = volatile inhalational; Pts = patients; TIVA = total IV anesthesia.

was done without replacement and within a tolerance limit of 0.00075. Chi-square method was used to compare the paired group, and Cox regression method stratified by matching pairs was used to fit the univariate models. Multivariable and subgroup analyses were repeated by using the same methodology.

Results

A total of 11,395 anesthetics using INHA or TIVA were delivered in the study period. After exclusions were applied, 3,316 patients remained in the INHA group and 3,714 in the TIVA group (fig. 1). Opioids were administered in all TIVA cases and in all but six of the INHA cases. Remifentanil

infusions were used in all patients in the TIVA group and in 697 of those in the INHA group. Patients received other opioids in 3,229 of 3,714 patients in the TIVA group and 3,273 of 3,316 in the INHA group. It was not possible to compare total amounts of opioid in the two cohorts due to the problem of comparing continuous remifentanil infusions with the intermittent dosing regimes of other opioids. In the INHA group, 632 patients received isoflurane and 2,509 patients received sevoflurane for induction and maintenance of anesthesia. One hundred seventy-five patients received both sequentially. Patient characteristics, diagnosis, and surgery details are summarized in table 1. The mean age was 57 yr and did not differ between groups ($P = 0.26$). We had incomplete data for height and weight. Body mass index was available in a total of 5,916 of 7,030 patients. There was no difference between TIVA and INH groups ($P = 0.26$). Patients in the INHA group were more likely to be male, have an ASA score of III or IV, have undergone more complex surgery, have had a blood transfusion, had an epidural, and more likely to have documented metastatic cancer at the time of surgery. These factors were all therefore included in our multivariable model. The frequencies and proportions of the different cancer subtypes in the groups were recorded and are available in Supplemental Digital Content 1, http://links.lww.com/ALN/B221, table 1.

One-year survival for all patients was 91.2% (95% CI, 90.6 to 91.8). For patients who received TIVA, 1-yr survival was 94.1% (95% CI, 93.3 to 94.8), whereas for the INHA group it was 87.9% (95% CI, 86.7 to 89.1). Kaplan–Meier survival curves for the two types of anesthesia are displayed in figure 2. Median follow-up for all patients was 2.66 yr (95% CI, 2.62 to 2.69), 2.51 yr (95% CI, 2.47 to 2.55) for TIVA and 2.91 yr (95% CI, 2.85 to 2.96) for INHA. The overall mortality rate was 18.5% (1,300 of 7,030), 13.6% (504 of 3,714) in the TIVA cohort and 24% (796 of 3,316) for INHA.

Overall survival from date of surgery against anesthesia type and other variables was compared separately in a univariate Cox model and subsequently in a multivariable Cox regression. Body mass index data were only available for 5,916 of 7,030 (84%) patients and hence was not included in the multivariable model to avoid excluding over 15% of the patients. The hazard ratio (HR) of the groups in the univariate model for the whole patient group and for the propensity-matched groups is shown in table 2. An HR greater than 1 represents an increased risk of death and less than 1 the reverse. Volatile inhalational anesthesia was associated with an HR of 1.80 (1.61 to 2.02) for the overall group on univariate analysis and an HR of 1.46 (1.31 to 1.64) after multivariable analysis for known confounders (table 3). Other variables associated with a significant increase in the hazard of death after multivariable analysis included age, male sex, blood transfusion, ASA score, and the presence of metastases at the time of surgery (table 3).

Propensity-matched Analysis

Propensity-matched analysis resulted in 2,607 patients in each group, with similar baseline characteristics (table 1). Volatile inhalational anesthesia was still associated with a raised HR in both univariate (1.59 [1.30 to 1.95]) and multivariable (1.46 [1.29 to 1.66]) analyses. The association of other variables with outcome was similarly unaffected.

Subgroup Survival Outcomes by Cancer Units, Severity of Surgery, Presence of Metastases, and ASA

A subgroup analysis was undertaken to assess the association of TIVA and INHA with outcome depending on specific cancer types and severity of surgery. Due to significant interaction with the type of surgery and metastases ($P = 0.005$) and ASA score ($P = 0.003$), additional subgroup analyses were performed for these variables. Factors or variables included in the fitted multivariable model are detailed in Supplemental Digital Content 1, http://links.lww.com/ALN/B221, table 2. These data are presented for the matched group as a forest plots in figure 3. Similar data for the overall group are found as Supplemental Digital Content 1, http://links.lww.com/ALN/B221, figure 1. This analysis demonstrated a significantly worse outcome in the INHA group for all severities of surgery except three (in which there was a trend), for patients scored ASA I to III and for patients with or without metastasis at the time of surgery (fig. 3). It also demonstrated significant changes in patients with gastrointestinal cancer after multivariable analysis.

Discussion

This retrospective analysis of 7,030 patients who had elective cancer surgery over a 3-yr period evaluated long-term survival in patients receiving general anesthesia with volatile inhalational gases compared with IV anesthesia using propofol and remifentanil. After propensity matching and adjustment for known confounding factors, we found an HR of 1.46 (95% CI, 1.29 to 1.66) for death in patients receiving a volatile inhalational anesthetic compared with TIVA. Patients had a worse outcome if they received volatile inhalational anesthesia no matter their ASA score, surgical severity, or whether they had recorded metastasis at the time of surgery. In multivariable analysis according to surgical specialty, survival for patients undergoing gastrointestinal surgery with volatile inhalational anesthesia was significantly worse than in the INHA group. Other variables associated with reduced survival on multivariable analysis included age, sex, ASA score, blood transfusion, and metastasis at the time of surgery.

Surgical resection of tumors has been demonstrated to cause a measureable release of cancer cells into the circulation.[4,5] Alongside this potential "seeding," and despite preoperative staging, micrometastases may be present distant to the tumor at the time of surgery.[22] The immune system, and in particular, cell-based immunity, that may otherwise protect against proliferation of these cells is suppressed at the time of surgery. Patients with low levels

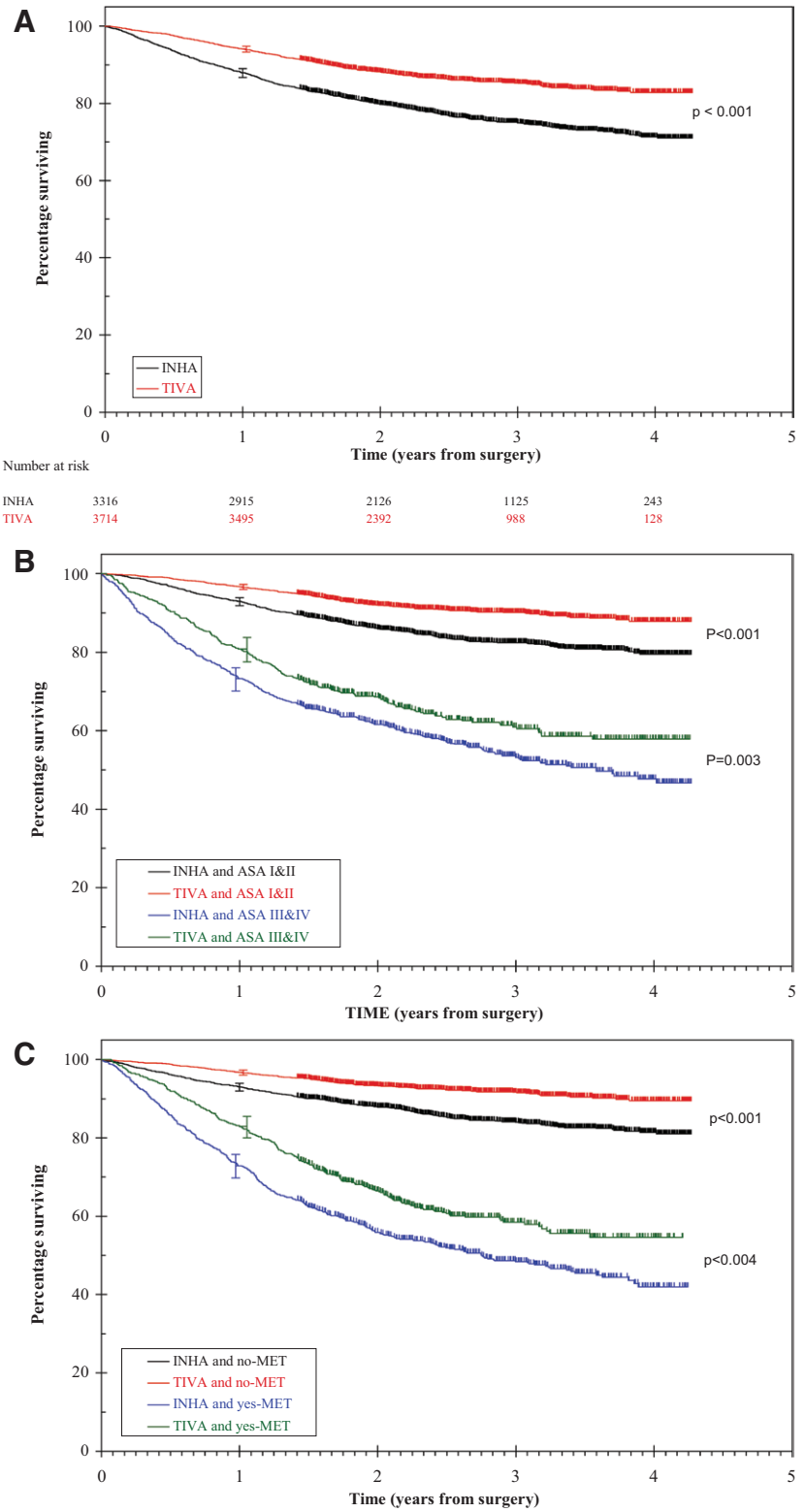

Fig. 2. (*A*) Overall survival curves from the date of surgery by anesthesia type, (*B*) by American Society of Anesthesiologists (ASA) score, and (*C*) by presence (or not) of metastasis. One-year survival for all patients was 91.2% (95% CI, 90.6 to 91.8). For patients who received total IV anesthesia (TIVA), 1-yr survival was 94.1% (95% CI, 93.3 to 94.8), whereas for the volatile inhalational (INHA) group it was 87.9% (95% CI, 86.7 to 89.1). The overall mortality rate was an 18.5% (1,300 of 7,030), 13.6% (504 of 3,714) in the TIVA cohort and 24% (796 of 3,316) for INHA. Median follow-up for all patients was 2.66 yr (95% CI, 2.62 to 2.69), 2.51 yr (95% CI, 2.47 to 2.55) for TIVA and 2.91 yr (95% CI, 2.85 to 2.96) for INHA. No-MET = no detected metastases at the time of surgery; Yes-MET = known metastases at the time of surgery.

Table 2. Cox Regression Proportional Hazard Survival: Univariate Model for Whole Group and Matched Group after Propensity Scoring

	Overall Patients			Matched Group (Stratified on Matched Pairs)		
Variables	Events/Total No.	HR (95% CI for HR)	*P* Value	Events/Total No.	HR (95% CI for HR)	*P* Value
Anesthesia type						
TIVA	504/3,714	1	< 0.001	407/2,607	1	< 0.001
INHA	796/3,316	1.80 (1.61–2.02)		597/2,607	1.59 (1.30–1.95)	
Age (continuous)	1,300/7,030	1.03 (1.02–1.03)	< 0.001	1,004/5,214	1.03(1.02–1.03)	< 0.001
Sex						
Female	728/4,434	1	< 0.001	572/3,228	1	< 0.001
Male	572/2,596	1.37 (1.23–1.53)		432/1,986	1.27 (1.12–1.43)	
Blood transfusion						
No	1,162/6,644	1	< 0.001	916/4,954	1	< 0.001
Yes	138/386	2.33 (1.95–2.78)		88/172	2.00 (1.60–2.49)	
Epidural use						
No	1,099/6,314	1	< 0.001	838/4,631	1	< 0.001
Yes	201/716	1.68 (1.45–1.95)		166/583	1.64 (1.39–1.94)	
ASA						
I	30/1,154	1	< 0.001*	21/773	1	< 0.001*
II	665/4,417	5.95 (4.13–8.58)	< 0.001	530/3,333	6.12 (3.96–9.47)	< 0.001
III	580/1,424	19.34 (13.36–27.91)	< 0.001	433/1,078	18.50 (11.94–28.68)	< 0.001
IV	25/35	56.84 (33.43–96.66)	< 0.001	20/30	50.62 (27.43–93.40)	< 0.001
Surgical severity						
1	145/631	1	< 0.001*	93/447	1	< 0.001*
2	637/3,668	0.75 (0.63–0.90)	0.002	525/2,625	0.96 (0.77–1.20)	0.706
3	207/1,489	0.57 (0.46–0.70)	< 0.001	167/1,226	0.61 (0.48–0.79)	< 0.001
4	311/1,242	1.10 (0.90–1.34)	0.363	219/916	1.14 (0.89–1.45)	0.291
Metastasis at surgery						
No	608/5,472	1	< 0.001	457/3,995	1	< 0.001
Yes	692/1,558	5.01 (4.49–5.58)		547/1,219	4.93 (4.36–5.59)	
BMI		n = 5,916			n = 4,402	
Under weight (< 18.5)	46/117	1.96 (1.45–2.65)	< 0.001	33/82	1.85 (1.30–2.64)	< 0.001
Normal (18.5–24.9)	519/2,217	1	< 0.001	402/1,654	1	0.001
Over (25.0–29.9)	370/2,171	0.70 (0.61–0.80)	< 0.001	290/1,627	0.72 (0.61–0.83)	< 0.001
Obesity (≥ 30)	237/1,411	0.68 (0.59–0.80)	< 0.001	180/1,039	0.68 (0.57–0.81)	< 0.001

* Overall categories comparison.

ASA = American Society of Anesthesiologists; BMI = body mass index; HR = hazard ratio; INHA = volatile Inhalational; TIVA = total IV anesthesia.

of perioperative natural killer cell activity have been demonstrated to have a worse outcome in a number of cancer types.[23,24] A number of perioperative interventions have been posited to affect cancer cell proliferation at the time of surgery. In particular, data derived from animal and *in vitro* models have suggested a role for opioids in the promotion of tumor cell survival and of angiogenesis. Although this has lead to the theory that regional anesthesia and the consequent minimization of opioid administration may lead to better cancer outcomes, clinical evidence is not conclusive.[9,10] Other interventions that have been suggested to have a beneficial impact impeding cancer cell growth in the perioperative period include the avoidance of blood transfusion and the use of cyclooxygenase-2 inhibitors, though again definitive clinical data are lacking.[25,26]

Ours is the first clinical study to show an association between volatile inhalational anesthesia and a reduction in long-term survival of cancer patients after multivariable analysis. Although this is not in any way proof of causation, there have been a number of animal and laboratory studies suggesting a biological mechanism for this association. Studies both *in vivo*[12] and more recently in patients undergoing surgery for breast cancer[13] have found a differential effect of volatile inhalational anesthesia and propofol on natural killer cell function, with the former being shown to result in a marked reduction. This could lead to the survival of tumor cells released into the circulation in the perioperative period. Research into organ protection in conditions of ischemia has demonstrated the up-regulation of the transcription factor HIF-1 with the administration of volatile inhalational anesthesia.[27] HIF-1 controls the adaptive response to hypoxia and governs the transcription of genes controlling cell proliferation, glucose metabolism, and angiogenesis with increases in vascular endothelial

Table 3. Cox Regression Proportional Hazard Survival: Multivariable Model for Whole Group and Matched Group after Propensity Matching

	Overall Patients		Matched Group	
Variables	HR (95% CI of HR)	*P* Value	HR (95% CI of HR)	*P* Value
Anesthesia type		< 0.001		< 0.001
TIVA	1		1	
INHA	1.47 (1.31–1.64)		1.46 (1.23–1.66)	
Age (continuous)	1.01 (1.01–1.02)	< 0.001	1.01 (1.01–1.02)	< 0.001
Sex		< 0.001		< 0.001
Female	1		1	
Male	1.30 (1.16–1.46)		1.334 (1.17–1.52)	
Blood transfusion		< 0.001		< 0.001
No	1		1	
Yes	1.47 (1.21–1.80)		1.59 (1.25–2.02)	
Epidural use		0.047		0.053
No	1		1	
Yes	1.22 (1.00–1.48)		1.26 (1.00–1.58)	
ASA				
I	1	< 0.001*	1	< 0.001*
II	4.01 (2.77–5.81)	< 0.001	4.05 (2.604–6.291)	< 0.001
III	9.62 (6.59–14.05)	< 0.001	9.50 (6.06–14.89)	< 0.001
IV	31.66 (18.32–54.71)	< 0.001	26.42 (14.02–49.76)	< 0.001
Surgical severity				
1	1	< 0.001*	1	< 0.001*
2	0.93 (0.77–1.12)	0.430	0.96 (0.77–1.20)	0.721
3	0.57 (0.46–0.71)	< 0.001	0.61 (0.47–0.79)	< 0.001
4	0.53 (0.42–0.67)	< 0.001	0.56 (0.42–0.74)	< 0.001
Metastasis at surgery				
No	1	< 0.001	1	< 0.001
Yes	4.04 (3.61–4.52)		4.15 (3.65–4.71)	

Only variables with significance level of 0.2 in the univariate analysis were used as candidate in the multivariable model. Similarly, BMI data are missing for more than 15% of the patients and were also not included in the multivariable model.

* Overall categories comparison.

ASA = American Society of Anesthesiologists; HR = hazard ratio; INHA = volatile inhalational; TIVA = total IV anesthesia.

growth factor (VEGF) production and erythropoietin gene expression.[28] However, HIF-1 also plays a role in the proliferation, angiogenesis, and metastasis of tumor cells through an increase in glucose uptake, VEGF expression, and cell protection from redox stress.[29] A recent study by Huang *et al.*[14] demonstrated that isoflurane at a clinically relevant concentration (0.5 to 2.0%) induced up-regulation of HIF-1α in a prostate cancer cell model. They found associated increases in tumor cell proliferation and migration and that isoflurane induced resistance to the chemotherapeutic agent, docetaxel. Sevoflurane has also been found to have an effect on HIF, with *in vitro* up-regulation in human glial stem cells.[30] Interestingly, in the study by Huang *et al.*, propofol inhibited HIF-1α activation induced by isoflurane and the subsequent changes in tumor cell behavior (including chemoresistance). There are a number of other studies supporting the notion that propofol inhibits its HIF-1α production.[31,32] Recent work in an ovarian cancer cell model has also demonstrated that isoflurane up-regulates expression of IGF.[15,33] IGF activates cellular signaling pathways that favor cell cycle progression and survival, and IGF receptors have been found to be increased in a number of tumors.[34] The same study found downstream increases in VEGF, promoting angiogenesis, and matrix metalloproteinases 2 and 9, both of which play a key role in degradation of the extracellular matrix, facilitating invasion and migration.

It could be speculated that this cancer cell proliferation, reduced apoptosis, and increased migration at the time of surgery, together with subsequent metastasis, could explain the clear separation in survival curves (which appears to continue to widen with time) between the volatile inhalational and IV groups seen in this study. The only other clinical study to consider outcomes for cancer patients receiving either propofol or volatile inhalational anesthesia was a retrospective analysis of 2,838 patients from a Swedish database. Survival for patients with breast (n = 1,837), rectal, and colon cancer was 4.7% higher at 1 yr and 5.6% at 5 yr in the propofol group, but after adjustment for confounders, the differences were not significant.[35] It is difficult to draw conclusions from this study as it includes

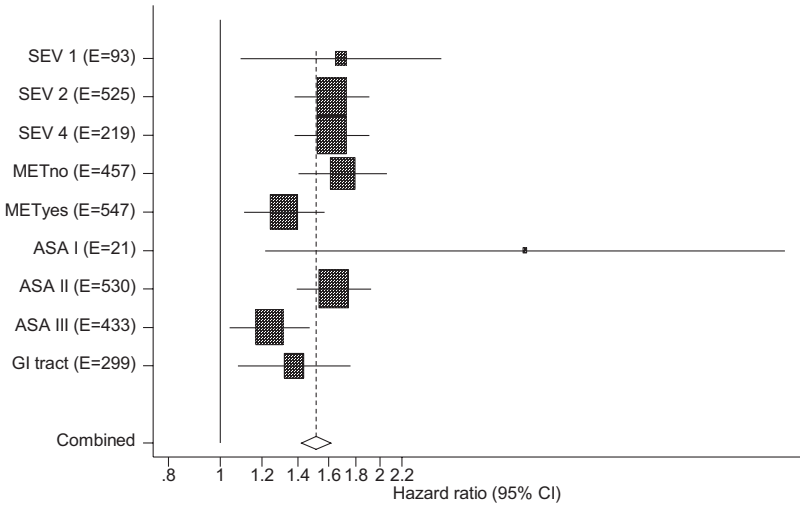

Fig. 3. Forest plot for the propensity-matched patient subgroup analysis showing multivariable (adjusted) hazard ratios; a subgroup analysis was undertaken to assess the association of total IV anesthesia and volatile inhalational (INHA) anesthesia with outcome depending on specific cancer types and severity of surgery. This analysis demonstrated a significantly worse outcome in the INHA group for all severities of surgery except 3 (which demonstrated a trend), for patients scored American Society of Anesthesiologists (ASA) I to III and for patients with or without metastasis at the time of surgery. Surgical severity was graded from 1 (least) to 4 (most) according to a scale derived by the National Institute for Health and Care Excellence. E = events; GI = tumors of gastrointestinal origin; METno = metastasis not present at time of surgery; METyes = metastasis present at time of surgery; SEV = severity of surgery.

patients treated over a 13-yr period with a likely change in baseline risk over this time period. During the study period, there was a change in practice with decreasing use of volatile inhalational anesthesia, which may also confound the results.

This is a large retrospective analysis for which the greatest criticism is that baseline characteristics of the two groups differ. Choice of anesthetic was per anesthetist preference, but there were more patients who were male, had an ASA score of III or IV, had metastatic cancer, and were having higher grade surgery in the volatile inhalational group. There was also a lower proportion of patients with breast cancer (who would be expected to have a better prognosis) in the INHA group. We have, however, performed propensity matching to correct for these factors as well as other potential confounders including among others, age, blood transfusion, and use of regional anesthesia. Subgroup analysis also confirmed preservation of effect specifically in those with higher ASA, more complex surgery, and with metastases. Analysis of cancer subgroups demonstrated a worse outcome after multivariable analysis in the gastrointestinal tumor group after propensity matching. Why we only found a difference in this subgroup is unclear. The most likely explanation relates to the relatively worse prognosis of gastrointestinal compared with other subtypes.

The noninclusion of staging data is also a potential confounder. Staging has a profound effect on outcome, but the data were for the most part unavailable as many patients were not formally staged before procedure. However, given its absence at the time of surgery, it is inconceivable to think that it would have influenced anesthetic preference. Finally, changes in cancer care over the period could influence the outcomes, but the study period was relatively short (3 yr) and the proportions of TIVA and volatile inhalational anesthesia remained very similar throughout.

From our analysis, it is not possible to definitively determine the reason for the difference between groups. It may be due to a negative effect of volatile inhalational anesthetic agents or a beneficial effect of propofol, a combination of both, or due to unaccounted for confounding factors. All of the patients in the propofol group also received an infusion of the ultrashort-acting opioid remifentanil, as did 697 of 3,316 patients in the INHA group. However, from these data, it is not possible to assess whether remifentanil had some contributory effect as all but six of the patients received opioids of some form and many of these agents have very similar effects.

Conclusion

This retrospective analysis of over 7,000 patients treated at a comprehensive cancer center demonstrates an HR of 1.46 (1.29 to 1.66) for death after multivariable analysis in patients receiving volatile inhalational anesthesia compared with IV anesthesia. There are many thousands of patients with a cancer diagnosis undergoing surgery every year, and in the context of biological plausibility and this analysis, it should lead to the urgent undertaking of prospective research to further evaluate our findings.

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Competing Interests

The authors declare no competing interests.

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