

ORIGINAL ARTICLE

## The choice of anaesthetic—sevoflurane or propofol—and outcome from cancer surgery: A retrospective analysis

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### Abstract

**Background.** Commonly used inhalational hypnotics, such as sevoflurane, are pro-inflammatory, whereas the intravenously administered hypnotic agent propofol is anti-inflammatory and anti-oxidative. A few clinical studies have indicated similar effects in patients. We examined the possible association between patient survival after radical cancer surgery and the use of sevoflurane or propofol anaesthesia.

**Patients and methods.** Demographic, anaesthetic, and surgical data from 2,838 patients registered for surgery for breast, colon, or rectal cancers were included in a database. This was record-linked to regional clinical quality registers. Cumulative 1- and 5-year overall survival rates were assessed using the Kaplan–Meier method, and estimates were compared between patients given propofol ( $n = 903$ ) or sevoflurane ( $n = 1,935$ ). In a second step, Cox proportional hazard models were calculated to assess the risk of death adjusted for potential effect modifiers and confounders.

**Results.** Differences in overall 1- and 5-year survival rates for all three sites combined were 4.7% ( $p = 0.004$ ) and 5.6% ( $p < 0.001$ ), respectively, in favour of propofol. The 1-year survival for patients operated for colon cancer was almost 10% higher after propofol anaesthesia. However, after adjustment for several confounders, the observed differences were not statistically significant.

**Conclusion.** Propofol anaesthesia might be better in surgery for some cancer types, but the retrospective design of this study, with uneven distributions of several confounders, distorted the picture. These uncertainties emphasize the need for a randomized controlled trial.

**Key words:** Anaesthetics, intravenous, inhalational, neoplasm recurrence, local, epidemiology, survival

### Introduction

There is converging evidence from animal studies and studies of human cell lines to indicate that different anaesthetics can have opposite effects on the immune system (1–7). Commonly used inhalational hypnotics, such as sevoflurane, are pro-inflammatory, whereas the intravenously administered hypnotic agent propofol is anti-inflammatory and anti-oxidative. A few clinical studies have indicated similar effects in patients (8–11). Against that background

it is not surprising that special interest has been paid to the effect of different anaesthetic techniques/procedures on cancer recurrence and patient survival after surgery (12,13).

Therefore, in this study we examined the possible association between survival from radical cancer surgery and the choice of hypnotic used, in a large cohort of patients undergoing cancer surgery between 1997 and 2010 at our hospital. We hypothesized that the 1- and 5-year survival rates after radical breast or colorectal cancer surgery under general anaesthesia

would be higher in patients given the intravenously administered hypnotic propofol than in patients given the inhalational hypnotic sevoflurane.

## Patients and methods

### Patients

Adult patients at least 18 years of age were operated on for breast or colorectal cancers under general anaesthesia from 1 January 1998 to 31 March 2010 at the Central Hospital in Västerås, Sweden. The Regional Ethics Committee approved the study on 21 January 2009 (2008/350). This investigation was carried out as a single-centre, register-based, retrospective cohort study.

### Data collection, extraction

Patients were identified from a computerized administrative system, which included some demographic, anaesthetic, and surgical data. Data were available for all patients exposed to anaesthesia and surgery during the defined period and included the choice of anaesthetic. All in all, 3,284 patients registered for surgery for breast, colon, or rectal cancers were extracted from the register (Figure 1). Further demographic, anaesthetic, and surgical data of interest, specified below, were extracted from patient records and included in a database.

### Registered data

*Descriptive data.* Sex, age, functional classification according to the American Society of Anesthesiologists (ASA) class, cardiac failure, cardiac ischemia, and any smoking habit.

*Anaesthesia-related data.* Use of propofol or sevoflurane (there were no restricting clinical guidelines for the choice), the use of adjuvant nitrous oxide (in use to the year 2000, mainly for breast surgery), any complementary epidural anaesthesia (for colorectal surgery), and the duration of anaesthesia.

*Surgery-related data.* Type of cancer removed, duration of surgery, blood loss, red blood cell (RBC) transfusion amount (number of units), tumour stage, complementary treatment used, date and type (local, regional, or generalized) of relapse of cancer, and date of death.

### Linking and matching of databases

The database was linked to the regional clinical quality registers at the Regional Cancer Centre (RCC) in Uppsala, Sweden, for confirmation of diagnosis and collection of tumour and clinical data. These registers have been found to be >97% complete, in comparison with the Swedish Cancer Register (SCR), to which reporting is mandatory by law. The SCR holds diagnoses only and contains no

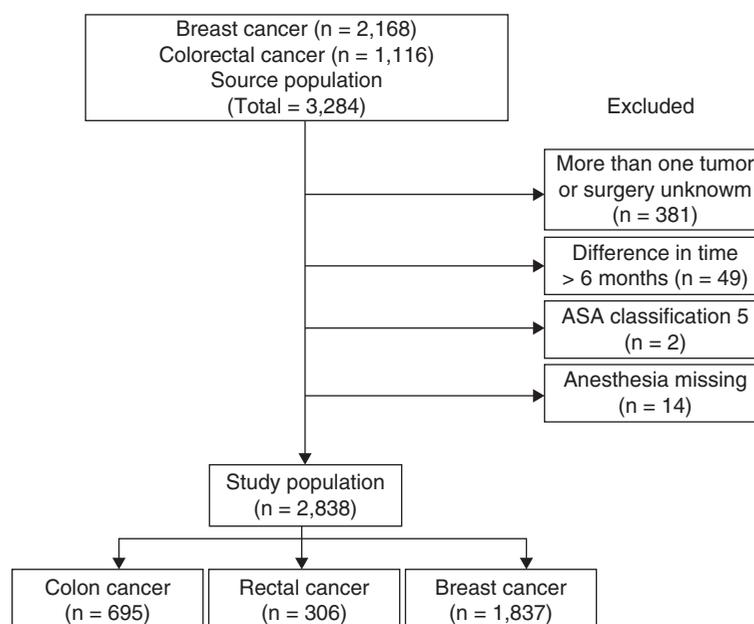


Figure 1. Study population.

clinical information. The RCC registers include detailed information on the mode of detection of the cancer, histopathology results, cancer stage at diagnosis, other prognostic markers, and any complementary treatment given. Hence, complete oncologic and outcome data were available for all types of cancer included in the study. Data on type and stage of the cancer and the patients' vital status were extracted, as well as different prognostic markers recorded in the oncologic registers.

For evaluating consistency, 476 patient records were double-checked for the rate of errors in data input.

### Analyses

The main end-point was overall survival rate, comparing patients given propofol or sevoflurane. Survival time was defined as the interval between date of surgery and date of outcome, emigration, or end of follow-up on 31 September 2012. Kaplan–Meier estimates of patient survival were calculated for each cancer site and between propofol and sevoflurane. Cox regression with hazard ratios (HR) and 95% confidence intervals (CI) were calculated to assess risk of death for each cancer site, adjusted for uneven distribution of potential confounding variables. In the next step, we calculated *relative survival*, which was calculated by dividing observed survival of the cancer patients with expected rate in the general background population with corresponding sex, age, and year of diagnosis. *Post hoc*, we also calculated the HR for each cancer site restricted to a follow-up period of 3 years. All *p* values were two-sided, and statistical significance was considered at  $p < 0.05$ . All analyses were performed using R version 10.2 (R Foundation for Statistical Computing, Vienna, Austria).

### Statistical power

A clinically relevant absolute difference in 5-year survival of 5% was hypothesized. With the original data set of 3,284 patients and our assumptions of standard deviations, we had a 90% power to detect a 5% difference at 5 years at  $p < 0.05$ .

### Results

After extraction of data from the patients' records, excluding technical and other errors in the administrative system, or those who were anaesthetized more than once with different anaesthetics (Figure 1), there were 903 patients anaesthetized with propofol and 1,935 with sevoflurane. One case of a wrong code for

the given anaesthetic was identified during double-checking of the data (476 files), which corresponded to a failure rate of 0.2%.

There was a shift over time towards a more frequent use of propofol (Table I). Thus, whereas less than 1% of the patients were given propofol during the first time-period (1997–2000), more than 85% were anaesthetized with propofol at the end (2007–2010) of the observation period. Sex and smoking habits were similar amongst the patient groups. Several potential confounders and effect modifiers were, however, found unequally distributed between the two anaesthetic groups: distribution of age at onset (colon;  $p < 0.01$ ), ASA class (colon;  $p < 0.01$ ), and a positive history of myocardial infarction (breast;  $p < 0.01$ ).

As regards perioperative characteristics (Table II), it was found that the duration of anaesthesia was similar when comparing the two anaesthetic procedures as was the use of epidural anaesthesia (not used for breast cancer patients but frequently used for colon and rectal cancer patients) and figures for blood losses. Nitrous oxide was used to some extent in sevoflurane-anaesthetized breast cancer patients. Surgery went on for about 5 hours in the rectal cancer patients, whereas surgery for colon and breast cancers was less time-consuming (somewhat more than 3 and 1 h, respectively). There were, however, no major differences in duration of surgery between the two anaesthetic procedures used. Some of the colon cancer patients (20%) were taken care of as emergency operations. Sevoflurane anaesthesia was then preferentially used. Almost half of the rectal cancer patients were re-operated at least once, whereas colon and breast cancer patients were re-operated less frequently (about 15% and 25%, respectively). At re-operation, sevoflurane tended to be used more frequently, also in patients primarily anaesthetized with propofol.

By use of Kaplan–Meier survival estimates there were differences observed in overall survival between patients anaesthetized with propofol and sevoflurane when data for all patients and cancer sites were combined (Figure 2). Thus, propofol-anaesthetized patients had a better overall survival ( $p = 0.004$ ; log rank test). More detailed analysis of the data, i.e. rates of relative survival, revealed that propofol anaesthesia had been of advantage for the 1-year survival of patients diagnosed with colon and breast cancer but not for that of patients with rectal cancer (Table III). After 5 years, however, there was no difference in survival for patients suffering from breast cancer (Table III). Those differences in overall 1- and 5-year survival rates for all sites combined were 4.7% ( $p = 0.004$ ) and 5.6% ( $p < 0.001$ ),

Table I. Demographic and clinical characteristics of patients operated for colon, rectal, or breast cancer between 1997 and 2010.

	Colon cancer		Rectal cancer		Breast cancer	
	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
All patients	179	516	104	202	620	1217
Calendar period						
1997–2000	1	201	0	75	4	367
2001–2004	80	200	45	73	124	696
2005–2007	50	81	28	44	222	136
2008–2010	48	34	31	10	270	18
Sex						
Male	85	259	60	121	3	3
Female	94	257	44	81	617	1214
Age at diagnosis						
<59 years	32	88	25	52	295	548
60–69 years	61	112	34	60	163	300
70–79 years	58	197	37	67	92	211
>80 years	28	119	8	23	70	158
Smoking history						
Never	110	253	58	86	417	593
Ex-smoker	40	89	29	42	67	94
Smoker	25	57	13	29	109	189
Cardiac failure						
No history	168	466	102	195	606	1164
Positive history	10	50	2	6	14	47
Cardiac ischemia						
No history	149	405	95	181	590	1112
Positive history	29	111	8	20	29	102
ASA classification						
1	18	52	21	32	182	384
2	114	261	61	123	355	630
3	42	175	21	45	77	178
4	4	28	1	2	4	17

respectively, in favour of propofol. The intergroup differences were strengthened when adding to the analysis all patients given the same anaesthetic for one or more repeated operations ( $n = 512$ ) (detailed data not shown).

However, following adjustment for confounders, the observed differences in overall survival were eliminated for all cancer sites (Table IV). A *post hoc* analysis of the HR restricted to a 3-year follow-up increased the difference between the two anaesthetic groups, but still lacked statistical significance. Thus, the HR for colon cancer decreased from 0.94 (95% CI, 0.71–1.25) to 0.86 (95% CI, 0.60–1.24) with propofol (HR for sevoflurane = 1.00).

## Discussion

There is converging evidence from animal studies and studies of human cell lines that different anaesthetics might affect the immune system in different ways (1–7). Thus, commonly used inhalational hypnotics such as sevoflurane are pro-inflammatory, whereas the intravenously administered hypnotic agent propofol is anti-inflammatory and anti-oxidative. Indeed, there are a number of clinical reports in support of this (8–11). More specifically, previous studies have demonstrated immunological effects of different anaesthetics on monocytes, macrophages, natural killer cells, cytotoxic T cells, and T helper cells (4–

Table II. Perioperative characteristics of patients operated for colon, rectal, or breast cancer between 1997 and 2010.

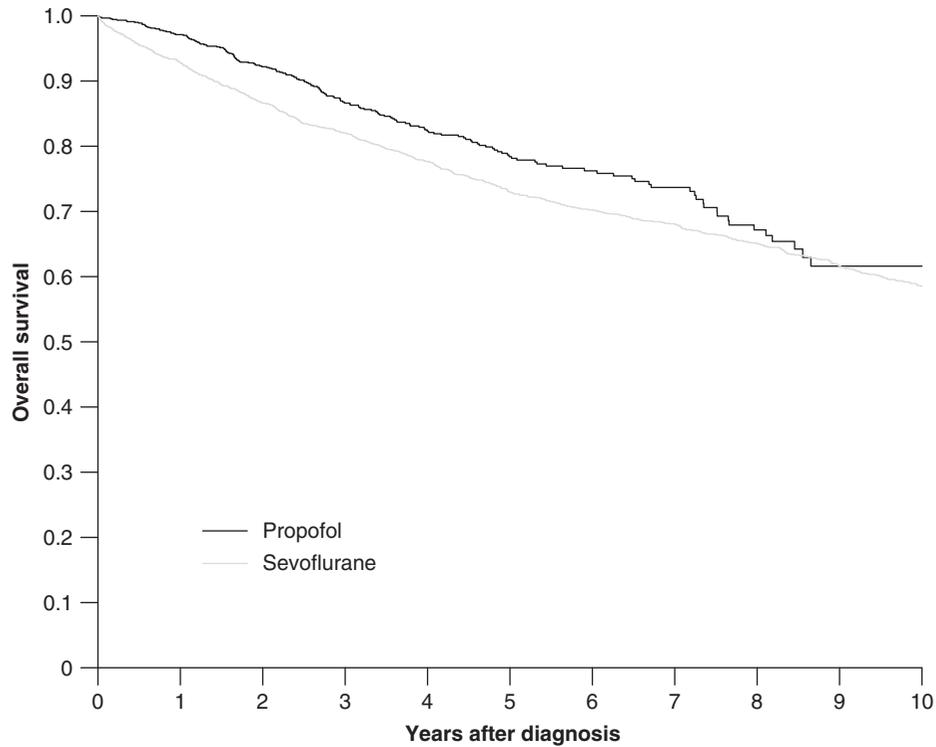
	Colon cancer		Rectal cancer		Breast cancer	
	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Duration of anaesthesia						
Mean (SD), minutes	253 (83)	230 (75)	366 (93)	349 (72)	119 (41)	110 (43)
Epidural anaesthesia						
No	11	88	2	5	620	1176
Yes	168	406	102	188	0	0
Nitrous oxide						
Yes	0	7	0	6	5	305
No	155	463	90	179	533	792
Blood loss						
Mean (SD), mL	350 (349)	375 (384)	815 (755)	857 (551)	85 (134)	137 (172)
Transfusions						
1	34	94	17	45	6	26
2	24	66	17	39	1	12
3	6	12	9	11	0	2
4+	1	10	7	5	1	3
Duration of surgery						
Mean (SD), minutes	204 (77)	185 (71)	309 (90)	294 (69)	86 (38)	80 (40)
Type of surgery						
Emergency	11	129	–	–	–	–
Elective	168	387	–	–	–	–
Re-operations						
No re-operations	148	453	59	124	480	891
One or more re-operations	31	63	45	78	140	326
Type of anaesthesia (during re-operation)						
Propofol	12	9	20	19	103	49
Sevoflurane	17	50	25	57	34	270
Other	2	1	0	1	1	5

6,10,14). By affecting T helper cells, anaesthetics indirectly affect the production of anti-inflammatory mediators such as interleukin-10. Anaesthetics also influence the production of pro-inflammatory cytokines such as tumour necrosis factor alpha and interleukin-1 and -6. Moreover, the effects could be indirect by blocking or not blocking the surgical stress response via the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (15,16). Thus, stress hormones such as catecholamines and cortisol will mediate inhibitory effects on immune functions. The neuroendocrine system, together with cytokines, augments these immunosuppressive effects in a highly complex way. Taken together, results from previous research support the hypothesis that inhalational

hypnotics are immunosuppressive in mice (6,17) as well as in humans (4,5).

There is also ample evidence to suggest that there are other adverse effects of inhalational hypnotics that could be attributed to immunological processes. For example, inhalational hypnotics seem to increase the occurrence of cancer metastases in mice and rats (6,7,17,18). Such adverse effects have, however, not been found for propofol. In contrast, propofol seems to inhibit tumour growth and reduce the tendency to induce metastases in mice (3,19).

It should also be kept in mind that genotoxic agents might impair patients' survival after cancer surgery because of the well-known connection between DNA damage and oncogenesis. The



No. at risk		0	1	2	3	4	5	6	7	8	9	10
Propofol	902	876	776	545	412	303	193	134	87	38	5	
Sevofluran	1935	1795	1660	1559	1446	1325	1186	1046	876	709	533	

Figure 2. Kaplan–Meier curve for survival after propofol- or sevoflurane-based anaesthesia for all cancer sites.

potential genotoxicity of inhalational anaesthetic agents in patients and in exposed staff in operating rooms has been studied both *in vitro* (20,21) and *in vivo* (22–25). Thus, a dose–response relationship between inhalational agent exposure and DNA damage has been suggested (25). Inhalational agents seem to be consistently genotoxic, whereas

the less studied propofol seems not to be so (22,24).

It was against this background that we planned our retrospective study. Just a few departments have applied a mixed use of hypnotics for a prolonged time-period, which has given us a unique opportunity to perform this type of comparative study. The use of

Table III. Proportions of 1- and 5-year survival for patients anaesthetized with propofol or sevoflurane and the difference between anaesthesia groups for patients diagnosed with colon, rectal, or breast cancer between 1997 and 2010.

	Propofol (95% CI)	Sevoflurane (95% CI)	Difference in survival (propofol minus sevoflurane) (95% CI)	
<b>1-year survival</b>				
All sites	0.97 (0.96–0.98)	0.93 (0.92–0.94)	0.04 (0.03–0.06)	<i>p</i> < 0.001
Colon cancer	0.93 (0.89–0.97)	0.84 (0.81–0.87)	0.09 (0.04–0.14)	<i>p</i> < 0.001
Rectal cancer	0.95 (0.91–0.99)	0.96 (0.93–0.98)	–0.01 (–0.05–0.05)	n.s.
Breast cancer	0.99 (0.98–1.00)	0.96 (0.95–0.97)	0.03 (0.01–0.04)	<i>p</i> < 0.001
<b>5-year survival</b>				
All sites	0.78 (0.75–0.82)	0.73 (0.71–0.75)	0.05 (0.02–0.09)	<i>p</i> < 0.01
Colon cancer	0.63 (0.56–0.72)	0.53 (0.48–0.57)	0.11 (0.02–0.20)	<i>p</i> < 0.05
Rectal cancer	0.73 (0.64–0.83)	0.67 (0.60–0.74)	0.06 (–0.06–0.17)	n.s.
Breast cancer	0.84 (0.81–0.88)	0.82 (0.80–0.85)	0.02 (–0.02–0.06)	n.s.

CI = confidence interval; n.s. = non-significant.



Table IV. (Continued).

	Colon cancer			Rectal cancer			Breast cancer		
	Univariate		Multivariate	Univariate		Multivariate	Univariate		Multivariate
	HR	(95% CI)	HR (95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Cardiac failure									
No history	-	-	-	-	-	1.00	Reference	1.00	Reference
Positive history	-	-	-	-	-	3.24	(2.51-4.19)	2.98	(2.17-4.11)
Anaesthesia duration	1.00	(1.00-1.00)	1.00	(1.00-1.01)	-	1.00	(1.00-1.01)	1.00	(0.99-1.02)
Blood loss	-	-	-	-	-	1.01	(1.01-1.01)	1.00	(1.00-1.00)
Stage at diagnosis									
I	-	-	-	-	-	1.00	Reference	1.00	Reference
II	-	-	-	-	-	2.97	(2.27-3.90)	2.61	(1.90-3.57)
III	-	-	-	-	-	8.57	(5.83-12.59)	5.67	(3.61-8.90)
IV	-	-	-	-	-	10.59	(6.13-18.29)	6.80	(3.61-12.85)
Nitrous oxide									
Yes	-	-	-	-	-	1.00	Reference	1.00	Reference
No	-	-	-	-	-	0.88	(0.70-1.10)	1.03	(0.72-1.46)

ASA = American Society of Anesthesiologists; CI = confidence interval; HR = Cox proportion hazard ratio; HR in *italic* = adjusted for propensity scores.

propofol, which was marketed later than sevoflurane, was uncommon to start with but increased over time, thus reducing the observation time for this group of patients. This also introduced time as a potential confounder, assuming that cancer care in general has improved in time (26). The overall mortality rate in our region for patients with breast, colon, or rectal cancer decreased by 7.6%, comparing the first (1997–1999) and last periods (2007–2009) in our study. It is difficult to estimate to what extent this general evolution in cancer care contributed to the better results for the propofol group.

Red blood cell (RBC) transfusions might have affected patient survival rates after cancer surgery, due to an immunosuppressive effect from such allogeneic material. Several possible mediators may be active: allogeneic mononuclear cells, white-blood-cell-derived soluble mediators, and/or soluble human leukocyte antigen peptides circulating in allogeneic plasma (27,28). We identified those patients having perioperative RBC transfusions, controlled the distribution between the two groups, and found no statistically significant difference.

Although increasing age and higher ASA class significantly affected outcomes in the regression model, the contribution of an uneven distribution of age and ASA class to the observed difference in outcome between the two anaesthetic groups was small, taking into consideration the relatively small numbers in the subgroups with the highest HR values (Tables I and IV). The higher proportion of emergency cases given sevoflurane for colon cancer was substantial (25.0% versus 6.1%). This contributed to the results in the multivariate analysis, and the difference in HR was 40% (Table IV). This is probably especially valid for the difference in 1-year survival rates, assuming that emergency surgery will affect short-term survival more. However, the difference between the two hypnotics in the 5-year survival was not inferior to the 1-year result: rather the opposite, which confuses the discussion.

Morphine use postoperatively inhibits the immune response (27,29,30). However, we have no reason to suspect an uneven administration of postoperative morphine to the two study groups. This was, however, not controlled for during data evaluation because we did not have access to the drug documentation system for the surgical wards. Synthetic opioids, such as fentanyl, alfentanil, and remifentanyl, all used intraoperatively, have been proven not to suppress the immune response (31,32). On the contrary, these synthetic opioids might have positive effects in this context (33).

Nitrous oxide is supposed to impair the immune defence, and it also impairs DNA production by

inhibition of the vitamin B<sub>12</sub> component of methionine synthetase (7,34,35). The authors of a prospective trial were unable to confirm any impact from nitrous oxide on survival after colorectal surgery (36). However, that trial had limited power, being aimed originally to study postoperative infections. Nonetheless, we stopped the use of nitrous oxide in the mid-1980s for a number of surgical procedures, among them abdominal surgery. However, we continued to use nitrous oxide until the year 2000 for breast cancer surgery (37). Therefore, nitrous oxide was a potential confounder for a part of our study population. Moreover, the distribution was highly skewed with 27.8% versus 0.9% in patients anaesthetized with sevoflurane or propofol, respectively. Nevertheless, the regression model indicated no contribution from nitrous oxide to the results.

Epidural anaesthesia might be beneficial for survival from cancer surgery (12,13,38). The proportion of patients given epidural anaesthesia for colon cancer was higher in patients given propofol—93.9% versus 82.2%—and the HR value could be interpreted to indicate a beneficial effect from epidural anaesthesia, but it was not statistically significant. The proportion of repeat operations was higher for patients with colon cancer in the propofol group (17.3% versus 12.2%). The impact of repeat operations on survival has not been investigated thoroughly, but it is reasonable to assume some impact. However, the number of patients involved was low.

Selection bias is an inherent major disadvantage in every retrospective study. Here, the risk was considered low because of the non-selective use of the hypnotics, with no guidelines directing the use of a certain drug to a specific group of patients. In all, there were 4.7% more patients with a positive history of myocardial infarction in the sevoflurane group (breast cancer surgery). This relatively small difference does not support the choice of sevoflurane for myocardial ‘protection’.

The Cox HR factor, calculated to assess the risk of death for each cancer site with adjustment of uneven distributions of potential confounding variables, included the whole observation period, which introduces the question of ‘over-adjustment’. Obviously, survival curves for two populations must meet at some point, and for patients with colon cancer this happened after 8 years. To reduce the impact of a time-span in which the two curves meet, we calculated the HR at 3 years after surgery. This increased the difference in survival between the two anaesthetic groups, but still without being statistically significant.

All in all, we found that patients anaesthetized with propofol had longer overall survival rates than patients anaesthetized with sevoflurane when data for all

patients and cancer sites were combined. However, this finding lost statistical significance after adjustment for confounders and effect modifiers. Thus, the results of our study do not support conclusions of other studies, claiming that survival might be higher after propofol anaesthesia. Based on the current results, we have made a power analysis for a prospective study. It was found that we will need at least 3,000 patients with colon cancer. This strongly indicates that the current study was underpowered, leaving us with a somewhat vague conclusion. Since undesired effects from anaesthesia on survival have strong relevance for overall cancer treatment, any factor that can affect survival in the order of 5% or more must be investigated. At some institutions, actions have already been taken by changing to propofol anaesthesia for cancer surgery, despite the lack of strong evidence (39). Therefore, we are obliged to plan for a randomized, prospective, controlled trial.

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