anesthesia (TIVA) or INHA is at the discretion of the individual anesthesiologist, and each surgeon habitually works with only one or two anesthesiologists. As each surgeon's patients will have distinct survival characteristics, their outcomes will also be strongly correlated with the anesthesiologist,[2] and hence also TIVA/INHA use. The differences reported by Wigmore *et al.* may, therefore, stem from differences in surgery, rather than the choice of anesthetic, that is, the type of anesthesia may be proxying the identity of the surgeon. (Including the surgeons' identity as a simple covariate or using a shared frailty Cox model would have reinforced their analysis.)

- *Timing*: The article's survival curves show that the differences between the groups of patients emerged in the first 9 months or so after surgery. Thereafter the curves appear almost parallel. Inclusion of CIs on the Kaplan–Meier plots would have made this clearer. The hypothesis implies that differences in mortality should appear later. So the authors' own data suggest that some other mechanism was responsible for the observed differences.
- *Choice of survival model*: We believe that the choice of a simple multivariable Cox regression model should have been examined more closely. Use of the Cox model makes a strong assumption that the hazard ratio remains constant with time, but this is inconsistent with both the hypothesis and the Kaplan–Meier plots. The authors should have tested the proportional hazard assumption, as the parameter estimates may be invalid. It might have been better to fit a piecewise Cox model with different hazard ratios before and after 9 months or use a fully parametric technique such as accelerated failure time regression.

Wigmore *et al.* have touched on questions of immense clinical significance. But we are not yet convinced that their data and analysis have implications for clinicians outside their own hospital. We agree with them that prospective research, with randomization of TIVA *versus* INHA, is needed.

Competing Interests

The authors declare no competing interests.

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Total Intravenous Anesthesia and Transfusion: A Double Whammy?

To the Editor:

I read with great interest the article by Wigmore *et al.*[1] at the Royal Marsden Hospital (London, United Kingdom), which suggested that total intravenous anesthesia (TIVA) is associated with improved cancer survival when compared to volatile inhalational anesthesia. The study has caused a great deal of excitement among many, and with good cause, demonstrating a 50% greater risk of mortality in the volatile group compared to TIVA.

I noticed that even after propensity matching, there was a statistically significant difference in transfusion rates between groups, there being an almost 50% higher rate of blood transfusion in the group receiving a volatile anesthetic (150 *vs.* 110 patients, $P = 0.011$). The reason for this difference is unclear; it may be that patients undergoing TIVA have lower rates of perioperative anemia, have less bleeding intraoperatively, or simply that anesthetists who use TIVA also have more conservative thresholds for blood transfusion.

It is recognized that conservative blood transfusion strategies may offer survival benefit,[2] and reducing the use of allogenic blood transfusion may improve mortality.[3] In fact, blood transfusion has been reported to worsen a variety of outcomes[4] in cancer surgery including increasing incidence postoperative infections and increasing disease recurrence in addition to increasing mortality.[4,5] Perioperative blood transfusion may influence immunomodulation in a number of ways,[6] including potentiating postoperative levels of the cytokine interleukin-6 and interleukin-6–inducible tumor growth factors such as hepatocyte growth factor and vascular cell adhesion molecule 1.[5] So potentially both blood transfusion and use of volatile may have contributed to reduce survival in the inhalational group *via* their impact on immunomodulation, thereby increasing cancer cell growth.

The magnitude of the TIVA survival benefit seen in the Royal Marsden study[1] can clearly not be explained by the differences in transfusion rates alone. In absolute terms, there were 190 more deaths in the propensity-matched volatile group, but only 40 more patients in that group underwent blood transfusion. However, I believe differing transfusion rates between groups may be an important confounding factor, which was not mentioned by the authors in their discussion. It is increasingly recognized that many aspects of anesthetic care,[7] including perioperative transfusion, use of opioid analgesia, and regional anesthesia, may all alter the immune response and

influence cancer recurrence and thus survival. Clearly the situation is far more complex than the headline; I do hope when prospective research is undertaken, it takes these wide-ranging aspects of perioperative care into account.

Competing Interests

The author declares no competing interests.

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Long-term Survival, All-cause Mortality, and Propensity Score Matching

To the Editor:

We read with great interest the article by Wigmore *et al.*[1] The authors have produced one of the largest studies published looking at cancer survival and anesthesia.

In an era where new cancer therapies are becoming ever more expensive to develop, their primary study finding, increase in mortality associated with inhalational anesthesia compared to intravenous anesthesia with an adjusted hazard ratio of 1.46 (1.29 to 1.69) after propensity score matching and multivariate analysis, is one of huge potential significance.

There are three points arising from the study we would like to discuss.

First, we agree with the authors that long-term survival is a key outcome measure in cancer surveillance. However, we noticed this study analyzed patients over a 3-yr period, with a further 18-month follow-up period, giving a maximum total potential follow-up time of 4.5 yr.

Widely accepted measures of long-term cancer survival are 5 and 10 yr.[2,3] We feel that the use of the phrase "long term" in the study title could mislead some readers. Perhaps it would have been more appropriately titled, simply, "survival rates for patients undergoing volatile *versus* intravenous anesthesia for surgery."

Second, we would like to highlight issues around the use of propensity scoring analyses and all-cause mortality data.

All-cause mortality is typically used as an outcome measure in prospective trials. Randomization helps account for unknown confounding factors affecting the outcome, thus facilitating the use of all-cause mortality as a primary outcome.

Usefulness of propensity scoring matching in retrospective studies is limited by the fact that remaining unmeasured confounding may still be present.[4] This makes the all-cause mortality data presented in this study more difficult to evaluate.

Preclinical studies in the literature suggest some form of immunomodulatory effects related to propofol or volatiles[5,6] during the intraoperative period affect the likelihood of recurrence of cancer.

Given this potential for causality combined with the limitations of propensity score matching, we suggest the study could be further refined by looking at cancer-related deaths only as opposed to all-cause mortality.

A possible suggestion would be obtaining mortality data from national cancer registries where cause of death would also be available, as an alternative to the National Health Service demographics service.

Finally, we noticed the Kaplan–Meier survival curves were for unmatched data only. We think that comparing the survival curves for the unmatched groups to those of the groups matched for known variables would add something to the study.

We acknowledge the authors recognized some of the inevitable shortcomings of retrospective studies and support their calls for urgent prospective work to corroborate their findings.

Competing Interests

The authors declare no competing interests.

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