Survival Advantage with Total Intravenous Anesthesia in Cancer Surgery: Is This Confounded by Cancer Type and Stage?

To the Editor:

We read with interest the article by Wigmore *et al.*,[1] in particular the impressive survival advantage associated with the use of total IV anesthesia (TIVA) compared to inhalational anesthesia. The study incorporated a propensity score–adjusted model, which is the most robust method to control for known confounding variables in observational studies. In addition, the authors present a biologically plausible mechanism, which satisfies a criterion for causality.

However, our main concerns relate to unmeasured confounders in the association between TIVA and cancer mortality. Type of cancer has been previously documented as an important determinant of survival. For example, 5-yr survival from breast cancer may be between 80 and 90%,[2] whereas for sarcoma, it is around 60%. Observing Supplemental table 1 shows imbalances in these baseline characteristics, which were not included in any propensity score–adjusted models. The values for breast cancer (18 *vs.* 42%; $P = 0.001$) and sarcoma (19 *vs.* 13%; $P = 0.001$) were both clinically and statistically significant.

Indeed, when the authors performed subgroup analyses, the only significant differences were observed in gastrointestinal surgery. This is alluded to in the limitations, with the authors highlighting the potential reason of higher mortality in this subgroup. However, a more nuanced explanation may be that once this important confounding variable is eliminated, the difference in survival between TIVA and inhalational anesthesia is lost. To substantiate their hypothesis, the authors cite a similar cohort study that compared propofol to sevoflurane. This study performed a multivariate analysis in specific cancer subtypes (breast, colon, and rectal), and the relationship was indeed lost on multivariate analysis.[3]

The authors also correctly state that not including staging in the model is a severe limitation and an additional confounder. We accept that these data may not have been available, although not including this casts further doubt over the validity of the findings. Similarly, other unknown preference biases influencing the attending anesthesiologist's decision to use a particular technique (confounding by indication) may affect the reliability of the author's conclusions.

In order to resolve the concerns highlighted above and clarify the results to the readership, we would ask the authors, is it possible to reanalyze your data in such a way that the important confounding variable of cancer type is accounted for? This could be achieved in two ways. First, cancer type could be used in the propensity-matched model to ensure an equal balance of cancer types between the TIVA and inhalational groups. Alternatively, if this is not possible, the fully adjusted results for each cancer type subgroup should be reported with their respective CIs to allow the reader to interpret the results once the confounding variable of cancer type is eliminated.

While the findings of this retrospective analysis are interesting, biologically plausible, and merit further investigation, we feel that resolving the doubts over these confounding variables is necessary before embarking on high-resource, prospective randomized studies investigating reductions in mortality with TIVA in patients undergoing surgery for cancer. If the findings are as reported, then the choice of TIVA over inhalational anesthesia confers a similar survival advantage when compared to Herceptin in the treatment of breast cancer.[4]

Competing Interests

The authors declare no competing interests.

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Missing Randomization ...

To the Editor:

Wigmore *et al.*[1] report "an association between volatile inhalational anesthesia (INHA) and a reduction in the long-term survival of cancer patients" and the hypothesis that "volatile inhalational agent in anesthesia may augment cancer cell growth."

We have three criticisms of the link between the hypothesis and the presented data.

- *Omission of important confounding*: In the United Kingdom, the choice of total intravenous

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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