

## 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.*,<sup>1</sup> 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%,<sup>2</sup> 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.<sup>3</sup>

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.<sup>4</sup>

### Competing Interests

The authors declare no competing interests.

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## Missing Randomization ...

### To the Editor:

Wigmore *et al.*<sup>1</sup> 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