Endpoint Selection and Unreported Analgesic Use May Render Oncologic Studies Inconclusive

To the Editor:

We read with great interest the article by Gottschalk *et al.*[1] and wish to congratulate them for their great and remarkable work. They showed that, although the use of epidural analgesia for perioperative pain control during colorectal cancer surgery was not associated with a lower rate of cancer recurrence, a potential benefit was observed in older patients. Their results were in contrast with those of Christopherson *et al.*,[2] whose study population was similar, apart from sample size.

Nevertheless, the primary endpoints of these two studies were different. Gottschalk *et al.*[1] reported the incidence of cancer recurrence whereas Christopherson *et al.*[2] found a difference in terms of survival.

However, the definition of cancer recurrence used by Gottschalk *et al.*[1] would be of interest. The application of their findings may be limited as a result of this omission. Establishing a diagnosis for local recurrence can be particularly difficult in rectal cancer patients. It is for this reason that researchers[3] often consider reported rates of recurrence in this population to be of limited value. In this study, readers are uncertain about study methodology, potential bias, and the incidence of cancer-related death in both groups (epidural *vs.* nonepidural). Therefore, the results of Gottschalk *et al.*[1] might best be considered inconclusive.

Moreover, epidural analgesia is not the only intraoperative variable that could influence cancer outcomes. In the study by Gottschalk *et al.*,[1] the epidural group presented with more rectal cancer, higher histologic grade, more frequent radiotherapy and chemotherapy, and more blood loss, suggesting more difficult surgeries. All these characteristics are potential confounding factors that may impact the rate of cancer recurrence. Even if multivariate analysis has been well performed, these patients' characteristics increases the risk that the epidural group includes other unknown negative factors. In addition, Gottschalk *et al.*,[1] do not make available data concerning the number of nodes removed or the quality of the mesorectum—both indicators of surgery quality.

Finally, another potential bias in this study is the intraoperative use of nonsteroidal antiinflammatory drugs. The overexpression of cyclooxygenase type 2 and the possible immunoprotective effect of these drugs may have an impact on long-term cancer recurrence.[4] It would be of interest to know if the groups are balanced for the use of these medications. Indeed, the older patients are often more prone to not receive nonsteroidal anti-inflammatory drugs. And the effect of the epidural analgesia might then have been unmasked for this reason. Following this hypothesis, in younger patients, these drugs may have masked the effect of epidural analgesia.

In conclusion, interpretation of the results reported by Gottschalk *et al.*[1] must wait until their methodology is further clarified.

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Epidural Analgesia and Cancer Recurrence: Timing Matters

To the Editor:

I read with great interest the recent publication in ANESTHESIOLOGY regarding the potential effect of epidural analgesia on cancer recurrence in patients undergoing colon surgery.[1] The study[1] reported that epidural analgesia showed no overall benefit—a finding that is in contrast to those of previous investigators.[2,3] However, Gottschalk *et al.*[1] report a limited beneficial effect in older patients as observed in *post hoc* analysis.

Is it possible that the results of the study by Gottschalk *et al.*[1] are different from those previously reported because their epidurals were not necessarily initiated before surgical incision? As a result of this methodologic preference, readers do not know whether these epidurals were functioning intraoperatively. This information is very important because, if the epidural was not used intraoperatively, suppression of the surgical stress response (and the resulting immunosuppression) may have not occurred in many of the patients in this study. In a similar study, Christopherson *et al.*[2] ensured that an analgesic level was attained before surgical incision—which may explain why an overall benefit was shown in that trial, but not in the current one.

Why patients older than 64 yr had some benefits remains uncertain. It could be a random statistical finding, as noted by the authors.[1] Alternatively, one can assume that these patients

may have received less narcotic than their younger counterparts—or that these patients take drugs that may play a role in cancer recurrence, such as β blockers and statins.[4]

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In Reply:

We thank our colleagues for their interest regarding our recent work.[1] In response to their inquiries, *recurrence* in our study was defined as any (local or metastatic) detection of colon cancer after primary resection. In the commonwealth of Virginia, treating physicians are required by law to report the cancer status of all patients. The University of Virginia Cancer Center, Charlottesville, tracks this data. Therefore, we are fortunate to have access to long-term follow-up cancer recurrence data on a large number of patients. However, we fully acknowledge that any retrospective study, including ours, is limited by (1) the accuracy of the available medical records, which may include missing data, and (2) difficulty controlling bias and confounding factors that could influence cancer recurrence (*e.g.*, α and β blockers, statins, nonsteroidal antiinflammatory drugs, cyclooxygenase inhibitors).

We agree with Dr. Tiouririne that intraoperative use of epidural analgesia (*i.e.*, to supplement general anesthetics) may have different effects on cancer recurrence than epidural analgesia used only postoperatively. As Christopherson *et al.*[2] note, a variety of factors influence cancer recurrence. For example, cancer stage and grade are almost always the best predictors of recurrence. Although our analysis corrected for major factors, our statistical modeling was, of course, restricted to the available data.

Both letters assert that our findings contradict those of Christopherson *et al.*[2] However, this interpretation of our results is inaccurate; neither we nor Christopherson *et al.*[2] found an overall (primary hypothesis) benefit of epidural analgesia. Unplanned *post hoc* subgroup analyses—including our observation that cancer recurrence was reduced in older patients who received epidural analgesia—are notoriously unreliable. Indeed, such analyses, when statistically significant at 0.05, have only a 57% chance of being replicated in an identical clinical trial.[3]

Although the idea that regional analgesia may reduce the incidence of cancer recurrence is exciting, it remains a hypothesis at this time—a question that can be answered only with prospective randomized clinical trials. Fortunately, several such studies are already in progress.

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Sublethal Spinal Ketamine Produces Neuronal Apoptosis in Rat Pups

To the Editor:

Sir, we read with interest the article by Walker *et al.* and the accompanying editorial view.[1,2] Undoubtedly, subarachnoid administration of large doses of ketamine produces neuronal apoptosis in newborn rats, as was eloquently demonstrated by this article. However, we would like to request further clarification regarding the statement "3 and 10 mg/kg produced increasing initial sedation, and higher doses were lethal." Unlike the corresponding article regarding the safety of intrathecal morphine in rat pups in the same issue,[3] no indication of calculated LD_{50} of intrathecal ketamine is given. We are not suggesting that similar dose response curves need to be constructed[4,5] but would welcome the publication of supporting data.

Rat pups were also exposed to smaller doses of intrathecal ketamine (0.1–0.3 mg/kg); again, no data on analgesic action or neuronal apoptosis are given. These doses (rather than more than 3 mg/kg) are the comparative and relevant equivalents commonly employed for caudal anesthesia.[6]

We have also some concerns regarding reporting of the apoptosis data.[1] First, the authors are assuming that the cells they are staining with active caspase-3 are indeed neurons without assessing the cell type. Second, the authors have