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