

# Anesthesia and Cancer Recurrence

## Context for Divergent Study Outcomes

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**I**ntraoperative mortality is now so low that its rate is hard to measure. In contrast, postoperative mortality remains common, with about 2% of United States surgical inpatients dying within a month—mostly of cardiovascular causes. Longer-term mortality is even more common, with about 5% of surgical patients dying within a year; among patients more than 65 yr of age (about a third of U.S. surgical patients), a staggering 1 in 10 patients are dead within a year of inpatient surgery.

The leading cause of long-term mortality is cancer. Even after apparently complete resection, postoperative cancer recurs in up to one third of patients—and it is usually metastatic disease that eventually proves lethal.<sup>1</sup> High mortality after cancer surgery begs the question of whether there is any aspect of anesthetic management that might reduce the risk of disease recurrence, because even a small benefit would potentially save many lives. The article by Yoo *et al.*<sup>2</sup> in this issue of *ANESTHESIOLOGY* addresses this matter.

It might seem intrinsically unlikely that any aspect of anesthetic management, lasting a matter of hours, could influence recurrence of cancer that occurs months to years later. But the perioperative period produces substantial biologic perturbations. For example, surgery produces intense stress that is characterized by activation of neural and inflammatory signaling pathways, suppressed cell-mediated immunity lasting up to 1 week, and release of proangiogenic factors—all of which impair natural killer cells, our major defense against cancer. Accumulating



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evidence suggests that these perioperative events might promote progression of minimal residual disease or creation of a premetastatic niche that traps circulating tumor cells, leading to clinical cancer recurrence.

The degree of biologic perturbation depends on the magnitude of the surgical insult. For example, in animal models, larger operations produce more metastases.<sup>3</sup> In murine orthotopic models of spontaneous postoperative metastasis, simple primary breast tumor resection does not progress to metastatic disease unless accompanied by the surgical stress and tissue injury of a laparotomy.<sup>4</sup> Consistent with this theory, minimally invasive surgery may reduce recurrence risk,<sup>5,6</sup> whereas postoperative inflammatory complications such as wound infection and anastomotic leak further increase the risk of cancer recurrence.<sup>7</sup>

Anesthetic management potentially influences long-term cancer outcomes.<sup>8</sup> *In vitro*, animal, and (mostly retrospective) clinical evidence supports three anesthetic approaches that might reduce cancer recurrence risk: (1) regional analgesia including neuraxial and paravertebral blocks; (2) anesthetic adjuvants such as  $\beta$ -adrenoceptor antagonists, nonsteroidal anti-inflammatory drugs, and intravenous lidocaine; and (3) propofol (*vs.* volatile) anesthesia. Overarching these anesthetic approaches is modulation of the neural–inflammatory signaling that accompanies surgical stress. We will focus on the third of these mechanisms.

Volatile anesthetics impair numerous immune functions including neutrophils, macrophages, dendritic cells, T-cells,

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and natural killer cells. Volatile anesthetics also upregulate hypoxia inducible factor 1 $\alpha$  and phosphoinositide 3-kinase-Akt pathway signaling and have antiapoptotic properties, all of which promote proliferation of minimal residual disease.<sup>9</sup> In contrast, propofol used for total intravenous anesthesia may be protective through its anti-inflammatory and antioxidant properties,<sup>10</sup> preserved natural killer cell function,<sup>11</sup> and inhibition of mammalian target of rapamycin, p53, p38 mitogen-activated protein kinase, and matrix metalloproteinase signaling.

Wigmore *et al.*<sup>12</sup> conducted a retrospective, propensity-matched cohort analysis of 7,030 patients who had various types of cancer surgery and reported improved overall survival in patients given propofol rather than volatile anesthesia (15.6% *vs.* 22.8% 5-yr mortality after surgery; hazard ratio, 0.68; 95% CI, 0.60 to 0.78;  $P < 0.001$ ). Their results are consistent with other retrospective studies that also report improved overall survival with propofol anesthesia for esophageal (N = 922),<sup>13</sup> gastric (N = 2,856),<sup>14</sup> and colon (N = 1,363)<sup>15</sup> cancer surgery. The results of Yoo *et al.*, also retrospective, in breast cancer surgery diverge in showing no benefit from intravenous propofol-based anesthesia (N = 5,331).<sup>2</sup> Their results, in turn, are supported by other retrospective studies that similarly report no difference in overall survival for breast (N = 2,645<sup>16</sup> and N = 1,217<sup>17</sup>), colorectal (N = 1,297),<sup>17</sup> and lung (N = 943)<sup>18</sup> cancer surgery. So far, there are no major randomized trials.

The obvious question is why available reports comparing volatile and intravenous anesthesia differ so much. The robust studies of Wigmore *et al.*<sup>12</sup> and Yoo *et al.*<sup>2</sup> were well powered, and both used sophisticated statistics to minimize confounding. We believe that both may be correct *in context*.

In Wigmore *et al.*,<sup>12</sup> there was no significant difference with regard to anesthetic technique for the subgroup of patients with breast cancer (Tim Wigmore, B.M., B.Ch., F.R.C.A., F.F.I.C.M., F.C.I.C.M., The Royal Marsden NHS Foundation Trust, London, United Kingdom; October 2018, written communication, n = 1,422). Wigmore *et al.*<sup>12</sup> and Yoo *et al.*<sup>2</sup> are thus consistent with respect to breast cancer surgery, with the overall survival differences in the study by Wigmore *et al.*<sup>12</sup> being driven by subgroups of patients requiring gastrointestinal and urologic surgery—that is, in patients requiring large surgical procedures that cause considerable tissue injury and provoke substantial neural and inflammatory responses.

Other studies that reported favorable long-term outcome with propofol–total intravenous anesthesia also evaluated patients having major surgery—namely, esophagectomy,<sup>13</sup> gastrectomy,<sup>14</sup> and colectomy.<sup>15</sup> Although tumor type may play a role, available data seem most consistent with the theory that the magnitude of surgical stress is a key driver. Consistent with this theory, the study by Lee *et al.*,<sup>19</sup> who only included patients having modified radical mastectomy (as opposed to more common smaller breast-conserving operations), is revealing: they reported significantly

improved recurrence-free survival with propofol–total intravenous anesthesia (hazard ratio, 0.55; 95% CI, 0.31 to 0.97;  $P = 0.037$ ) compared with volatile-based anesthesia. Unfortunately, neither Wigmore *et al.*<sup>12</sup> nor Yoo *et al.*<sup>2</sup> explored the impact of anesthetic technique on long-term outcomes in patients having mastectomy independent of those having breast-conserving surgery.

Available data thus suggest that to the extent that propofol–total intravenous anesthesia reduces cancer recurrence and improves survival, benefit is most probable in patients having major cancer surgery. Similarly, adjuvant strategies targeting neural and inflammatory signaling (*e.g.*, neuraxial analgesia,  $\beta$ -blockers, nonsteroidal anti-inflammatory drugs, *etc.*), if helpful, are most likely to demonstrate benefit in patients having major rather than minor cancer surgery. Trials comparing cancer recurrence and survival with volatile and intravenous anesthesia for major cancer surgery are already in progress and are well worth doing, because even small reductions in cancer recurrence would save countless lives—and that from an intervention that is essentially cost-free and trivial to implement.

## Competing Interests

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