Is choice of anesthesia during cancer surgery linked to outcome?

By Patrice Wendling

The anesthesia and analgesic technique used during cancer surgery is rarely on patients’ radar, but an emerging body of evidence suggests it may affect their chances of recurrence and metastasis.

“There’s enough data to raise a concern, absolutely,” said Dr Hugh Hemmings, chair of anesthesiology at Cornell University, New York, and coeditor of a recent British Journal of Anaesthesia (BJA) special issue on anesthesia and cancer.

Laboratory studies in the 1980s and 1990s that suggested a link between anesthesia and cancer outcomes went largely unnoticed until a 2006 retrospective cohort study showed a 40% reduction in recurrence during 2.5–4 years of follow-up in women who were given paravertebral anesthesia, a type of regional anesthesia, with general anesthesia rather than general anesthesia and postoperative morphine analgesia during primary breast cancer surgery.

“It precipitated an explosion,” said Dr Donal Buggy, professor of anesthesiology at University College Dublin and coauthor of the 2006 study and BJA special issue. “Before that, the hypothesis that what we do perioperatively might influence cancer recurrence hadn’t been articulated. It is now the number 1, hot topic of research in our specialty.” The American Society of Anesthesiologists published its own special issue on cancer and anesthesia and debated the subject at a recent meeting. Experts in the field also convened last year in Dublin to review the state of the evidence and set future research priorities.

Positive and negative trial findings have caused some confusion among anesthesiologists, while oncologists and cancer pain specialists are largely unaware of the evidence, according to both men. In that regard, the BJA special issue serves as something of an opening salvo, calling for comment and collaboration from other specialists and badly needed funding for prospective clinical trials.

Stress response and immune function

The understanding that surgery induces a stress response and that stress can influence cancer outcomes has prevailed for decades. The breast study, however, suggested that regional anesthesia might preserve immune function by attenuating the surgical stress response and reducing the need for opioids.

A pair of studies in the BJA special issue show that serum from women who were given propofol general anesthesia with a paravertebral block for primary breast cancer surgery caused greater apoptosis, or programmed cell death, in breast cancer cells than did serum from women who were given standard sevoflurane general anesthesia with opioid analgesia.

In patients undergoing colon cancer surgery, epidural anesthesia has been shown to reduce the expression of angiogenesis-promoting factors such as vascular endothelial growth factor C, transforming growth factor beta, and interleukin-6.

“In a way it’s odd. How the heck does anesthesia affect cancer outcomes?” commented Dr James Rathmell, a cancer pain specialist and executive vice chair of anesthesia at Massachusetts General Hospital in Boston. “At first, nobody believed the observations, but now it’s starting to make some mechanistic sense.”

The role of opioids

A common theme running through much of the research is that any anesthetic technique that reduces the opioid dose also reduces the potential for cancer recurrence after surgery. That’s something that spans the actual surgery and the early postoperative period, Dr Hemmings said.

A small retrospective analysis of 99 consecutive patients with non–small-cell lung cancer found an association between higher doses of opioids in the first 4 days after thoracoscopic surgery with lobectomy and recurrence within 5 years.

There is some controversy, however, over whether the opioids are directly promoting metastasis in tumors or whether they are having an indirect effect on the immune system, which is affecting the ability of natural killer (NK) cells to fight perioperative metastasis, he said.

Dr Buggy’s group and others have data to suggest that the more cancer cells are exposed to opioids, the
more virulent the cancer cells are, and that patients with more virulent cancers have more mu-opioid receptors on their cells.

The influence of epidural anesthesia and opioids has resulted in conflicting results in prostate cancer. The reason is not clear, but it’s fair to say that the role of the immune system varies among cancer types, or even between cancer subtypes, and that some tumors elicit a more robust immune response, Dr Hemmings said.

“Maybe once we know more about the genetics of different types of cancer, we might be able to predict, based on the genomics of a particular patient, whether [that patient] will be more or less likely to be affected by a particular anesthetic technique or drug,” he added.

Although it is understood that opioid drugs are not good for the immune system, it will likely take a decade to piece together the various mechanisms at play, according to Dr Rathmell. Even then, the effect size of various anesthetic drugs and opioids on outcomes may be small and difficult to tease out in a prospective clinical trial given today’s rapidly changing landscape of oncology treatments and surgical techniques.

The answer to the hypothesis may well be “no,” but it’s certainly worth finding out, Dr Buggy countered. “Even if a randomized trial were to show a benefit of only 10%, it could be implemented worldwide very quickly and, importantly, at zero cost to patients because it would be an improvement in the risk of recurrence without side effects. Whatever the oncologists say, no matter how good their drugs are, and they are good, and no matter what great new drugs they come up with, and I’m sure they will, none of them will be without side effects and by golly, they’ll come with a big price tag.”

Cautioning against overstepping the evidence

In an accompanying BJA consensus statement, Dr Buggy, Dr Hemmings, and other experts in the field make clear that the evidence so far is hypothesis generating and insufficient to support any change in practice.

Dr Buggy said he resisted going public on the issue

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**Commentary** Toward a new alliance between surgeon and anesthesiologist

As anesthesiologists create an increasingly safe perioperative environment essentially devoid of fatal "never events" such as unrecognized esophageal intubation, local anesthetic toxicity, and oxygen supply failure, the focus of the field’s research activities has expanded to include the impact of anesthesiology care on outcomes long after the day of surgery. Concurrently, surgical research has demonstrated that the body’s response to stress may be responsible for our most daunting patient complications: venous thromboembolism, myocardial infarction, cognitive dysfunction, and acute kidney injury. The important data presented here demonstrate that cancer progression mediated by the body’s stress response may be affected by techniques that decrease the body’s perception of the surgical insult.

This is an important topic that has an impact on the field of perioperative medicine on several fronts. First, the path for future surgical and anesthesiology research must continue to increase its focus on stress response and its impact on postoperative outcomes. Despite disappointing early returns from studies evaluating steroid therapy in cardiac surgery, surgical researchers must continue to consider ways to decrease the impact of the surgical event through minimally invasive techniques, preoperative preparation, and perioperative pharmacology. Similarly, anesthesiology researchers must further efforts to incorporate novel procedures that preemptively decrease the body’s sensation of the surgical procedure. This may include peripheral nerve blocks, pharmacologic therapy, and targeting anesthetic endpoints other than consciousness.

— Sachin Kheterpal, MD, MBA

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Next, surgeons and anesthesiologists must break down historical perceptions and barriers to effective patient-focused teamwork in the operating room. Anesthesiologists will have to broaden the definition of a “successful anesthetic” beyond a patient delivered safely to the recovery room spontaneously ventilating and free of pain and nausea. As the science of stress response and cancer progression evolves, they must hold themselves to a higher standard focused on long-term patient outcomes, even if the techniques required are outside of their historical comfort zone. They must also encourage care processes that involve the surgeon in specific analgesic regimens, such as surgeon-placed perineural catheters during surgical dissection. Surgeons must evolve their demands of anesthesiologists beyond just patient safety and efficiency. The anesthesiologist can be a real partner in outcomes historically described as “surgical outcomes.”

This partnership requires communication and may require additional time during the preoperative or intraoperative anesthesiology induction period. Historically, the time from patient in room to anesthesia induction end was typically perceived as “overhead,” but it may reveal to be a time when procedures crucial to cancer progression may be performed.

Overall, these changes will create a unique and rewarding partnership in the operating room, research space, and administrative lounges. With a shared focus on long-term outcomes, the surgeon and anesthesiologist will realize the value of why they became doctors in the first place.
for years, fearing it would be misconstrued or oversold by the media and lead some cancer patients to demand specific anesthetic strategies for which causal links have yet to be established. “What we’re discussing here are great ideas, but that’s all they are. We do not have enough evidence to ask people, to suggest to people, or to make people feel guilty [and] that they should be changing their practice.”

Some physicians are already using paravertebral blocks and opioid-sparing techniques, but are doing so for reasons other than cancer recurrence, such as reduced side-effects or shorter hospitalization, Dr Buggy and Dr Rathmell said.

The emerging evidence, however, could have unintended consequences for the treatment of cancer pain, said Dr Jyoti D Patel, an oncologist with the Robert H Lurie Comprehensive Cancer Center at Northwestern University in Chicago. “This series of papers is compelling because . . . it sheds light on something that is currently under the radar and controversial. In particular, the study of opioid use postoperatively is intriguing, but we as physicians must also be careful not to undertreat postsurgical pain. Undertreatment of pain is associated with delays in recovery, fatigue, and depression.”

Dr Rathmell agrees. “The risk is that people will try to do all these opioid-sparing techniques, and we end up markedly undertreating pain.”

The path ahead

The absence of a definitive prospective randomized clinical trial in humans has hampered funding and fueled skepticism, but no fewer than 10 prospective trials are currently underway.

Recruitment is almost halfway complete for a 2,000-patient trial randomizing women undergoing primary nonmetastatic breast cancer surgery to propofol general anesthesia plus paravertebral block or general anesthesia plus morphine. A second large trial is evaluating disease-free survival, NK-cell function, immune function markers, and pain in patients undergoing thoracotomy for primary lung cancer randomized to combined epidural-general anesthesia or general anesthesia plus postoperative morphine.

The expert panel was reluctant to make any strong recommendation on what specific cancer should be studied next, with stakeholders in each area advocating for their own cancer model. Unanimity was not achieved, and the consensus statement makes a specific recommendation only for further evaluation on the effects of intravenous lidocaine and nonsteroidal anti-inflammatory drugs and cancer recurrence.

Politics has also played a part in study funding, which has been slow to come because anesthesiologists are outsiders to oncology’s inner circle, Dr Buggy noted. “The concept that Cinderella could go to the ball, that anesthesiology could actually have something that would perhaps change practice is something that a lot of people would be skeptical about before they get into the science. It’s a revolutionary idea.”

Disclosures: Dr Hemmings is an editor of the BJA and of Anesthesiology. Dr Buggy is a member of the BJA editorial board and has received research grant funding from Air Liquide, manufacturer of medical gases including xenon. Dr Rathmell is an executive editor for Anesthesiology. Dr Patel has no conflicts of interest.

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