Surgery remains a primary treatment for cancer. It is therefore important to know whether any perioperative factors, including anesthetic(s), can positively or negatively affect the prognosis of cancer. In this issue of Anesthesiology, Benzonana et al. have reported the effects of anesthetic isoflurane on the growth and migration (malignant potential) of renal cancer cells.

The debate on whether anesthetics and other associated perioperative events can influence the long-term prognosis of cancer patients who undergo surgery has been steadily gaining momentum in recent years. Several retrospective studies have suggested that resection of cancers by surgeries with regional anesthesia could be associated with better outcomes as compared those with general anesthesia in several types of cancer, including breast, colon, prostate, and ovary. In particular, Lin et al. have shown that patients who had radical prostatectomy with epidural anesthesia have a 57% lower recurrence rate as compared with those who had the radical prostatectomy with general anesthesia. However, contradictory clinical reports also exist, and it is therefore urgent to perform more clinical studies to determine the role of anesthesia in the outcomes and prognosis of cancer.

An early study has shown that general anesthetics such as halothane and nitrous oxide might accelerate postoperative metastasis (even to the organs in which they are not usually found) in lung cancer and melanoma in murine models.

A recent study has suggested that volatile anesthetics could affect gene expression in human breast and brain tumor cell lines. However, the further characterization of the effects of anesthetics on cancer growth and metastasis and the underlying mechanisms remain to be determined. Specifically, there has been a need to more clearly define the impact of the various anesthetic and analgesic agents on the risk of developing postoperative tumor recurrence or metastases, and there have been calls for researchers to offer greater clues as to the likely etiology of such findings. To date, those clues are largely centered around how anesthetics modulate various arms of the immune system, the neuroendocrine system, and the stress response that inevitably accompanies surgery.

Benzonana et al. offer a fresh perspective in which they report that isoflurane, a commonly used inhalation anesthetic, can act on cancer cells and the signaling pathways directly in a way that enhances the malignant and metastatic potential of the cancer cells. An article based on these findings has been published in this issue of Anesthesiology.

They focused on hypoxia-inducible factors (HIFs)—ubiquitously expressed transcription factors that regulate cellular oxygen homeostasis and govern the expression of hundreds of genes that work together to ensure a cell’s survival and adaptation to its environment. Such an integral role in the cell’s survival apparatus makes HIFs an attractive target for cancer cells to take advantage of; indeed high levels of HIFs are the feature of most solid cancers, and the
cancer cells with higher levels of HIFs tend to have poorer prognoses.

In a series of elegant studies, Benzonana et al. exposed renal carcinoma cells to a clinically relevant concentration (0.5–2%) of isoflurane for 2 h, and they found that isoflurane increases the levels of both HIF-1α and HIF-2α. They argue that this increase may further enhance those cells’ competitive advantage over their healthy neighbors, at a crucial time in the patient’s disease course of perioperative immune suppression, pain, and stress, ultimately leading to more aggressive behavior of these cancer cells.

First, they have found that isoflurane increases protein levels of HIF-1α and HIF-2α in renal carcinoma cells in a dose- and time-dependent manner. Moreover, isoflurane makes HIF-1α move to the nuclei of the cells. These findings suggest that iso-flurane may influence cancer prognosis through HIFs. Second, they have shown that isoflurane can induce phosphorylation of Akt in the renal carcinoma cells. These findings suggest that isoflurane increases the levels of HIFs by the enhancement of HIF generation. Third, isoflurane has been shown to increase the proliferation of renal carcinoma cells. Importantly, isoflurane does not induce cell death in these cells. Finally, the isoflurane treatment has been shown to increase cell migration in the renal carcinoma cells and to change the structure of the cells, which leads to more aggressive behavior of these cells.

Collectively, these findings suggest that isoflurane could promote a cellular mechanism (HIFs), which is implicated in tumorigenesis, and iso-flurane might enhance the cellular activities that are associated with a malignant phenotype in the cells.

Note that isoflurane has been shown to induce cell death, rather than increase growth of cells, in other studies.8–15 Therefore, as suggested by other studies, it is possible that isoflurane may have a dual effect on cell death, which is dependent on specific cell lines, various treatment time, and different concentrations.16,17

Nevertheless, the well-designed and well-performed study by Dr. Daqing Ma’s group is a timely and welcome starting point, grounded in sound and reasoned biochemistry at the cellular level, which could direct and focus the endeavors of much-needed in vitro and clinical follow-up work. The clinical evidence on the subject is limited to small-scale, often retrospective studies and is, at times, conflicting, with regard to how true or sizeable this concern is or how much of a difference that an anesthetic technique can make toward a patients’ long-term disease-free survival. Of course, what is sorely missing at this moment is a good number of randomized controlled trials that have adequate power and follow-up, but such are the number of variables in the perioperative period and such is the heterogeneity of “cancer” as a disease that accounting for each of these will be a difficult and costly challenge. Basic science studies such as the one by Benzonana et al. published in the current issue of Anesthesiology are essential for more in vitro and in vivo studies with different cancer cell lines and different anesthetics to be launched in this field. The current and future research findings would ultimately help to design clinical trials to explore good anesthetics/anesthetic technique for cancer patients.

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References
3. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI: Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105:660–4

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