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Cancer Prognosis: Can Anesthesia Play a Role?

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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 [1].

The debate on whether anesthetics and other associated perioperative events 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 under regional anesthesia could be associated with better outcomes as compared to those under general anesthesia in several types of cancer, including breast, colon, prostate and ovary [2–5]. In particular, Lin *et al.* have shown that patients who had radical prostatectomy under epidural anesthesia have a 57% lower recurrence rate as compared to the patients who had the radical prostatectomy under general anesthesia [5]. 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 halothane and nitrous oxide might accelerate postoperative metastasis (even to the organs in which they are not usually found) of lung cancer and melanoma in murine models [6]. A recent study has suggested that volatile anesthetics could affect gene expression in human breast and brain tumor cell lines [7].

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 post-operative 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 upon cancer cells and the signaling pathways directly in a way that enhances the malignant and metastatic potential of the cancer cells. A manuscript based on these findings has published in this issue of *Anesthesiology*.

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They focus 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% to 2%) of isoflurane for two hours, and they found isoflurane increases 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 with a dose- and time-dependent manner. Moreover, isoflurane makes HIF-1α move to the nuclei of the cells. These findings suggest that isoflurane 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 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 of these cells.

Collectively, these findings suggest that isoflurane could promote a cellular mechanism (HIFs), which is implicated in tumorigenesis, and isoflurane 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 then increase growth of cells, in other studies [8–15]. Therefore, 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, as suggested in other studies [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 vivo* and clinical follow-up work. The clinical evidence on the subject is limited to small-scale, often retrospective studies and is, at times, conflicting, in regards to how true or sizeable this concern is or how much of a difference anesthetic technique can make towards a patients' long-term disease-free survival. Of course, what is sorely missing at the 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

1. Benzonana LL, Perry NJS, Watts HR, Yang B, Perry IA, Coombes C, Takata M, Ma D. Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential *via* the hypoxia inducible factor cellular signaling pathway *in vitro*. Anesthesiology. 2013; XXX:XXX–XXX.
2. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: A variation associated with choice of anesthesia. Anesth Analg. 2008; 107:325–32. [PubMed: 18635504]
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. [PubMed: 17006061]
4. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: A retrospective analysis. Anesthesiology. 2008; 109:180–7. [PubMed: 18648226]
5. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: A retrospective analysis. Br J Anaesth. 2011; 106:814–22. [PubMed: 21436156]
6. Shapiro J, Jersky J, Katzav S, Feldman M, Segal S. Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. J Clin Invest. 1981; 68:678–85. [PubMed: 7276167]
7. Huitink JM, Heimerikxs M, Nieuwland M, Loer SA, Brugman W, Velds A, Sie D, Kerkhoven RM. Volatile anesthetics modulate gene expression in breast and brain tumor cells. Anesth Analg. 2010; 111:1411–5. [PubMed: 20889943]
8. Xie Z, Dong Y, Maeda U, Alfille P, Culley DJ, Crosby G, Tanzi RE. The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid beta protein levels. Anesthesiology. 2006; 104:988–94. [PubMed: 16645451]
9. Xie Z, Dong Y, Maeda U, Moir RD, Xia W, Culley DJ, Crosby G, Tanzi RE. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid β-protein accumulation. J Neurosci. 2007; 27:1247–54. [PubMed: 17287498]
10. Zhang Y, Dong Y, Wu X, Lu Y, Xu Z, Knapp A, Yue Y, Xu T, Xie Z. The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. J Biol Chem. 2010; 285:4025–37. [PubMed: 20007710]
11. Zhang Y, Xu Z, Wang H, Dong Y, Shi HN, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. Ann Neurol. 2012; 71:687–98. [PubMed: 22368036]
12. Istaphanous GK, Ward CG, Nan X, Hughes EA, McCann JC, McAuliffe JJ, Danzer SC, Loepke AW. Characterization and quantification of isoflurane-induced developmental apoptotic cell death in mouse cerebral cortex. Anesth Analg. 2013; 116:845–54. [PubMed: 23460572]
13. Yan H, Xu T, Zhao H, Lee KC, Wang HY, Zhang Y. Isoflurane increases neuronal cell death vulnerability by downregulating miR-214. PLoS One. 2013; 8:e55276. [PubMed: 23408966]
14. Brambrink AM, Back SA, Riddle A, Gong X, Moravec MD, Dissen GA, Creeley CE, Dikranian KT, Olney JW. Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Ann Neurol. 2012; 72:525–35. [PubMed: 23109147]
15. Shu Y, Zhou Z, Wan Y, Sanders RD, Li M, Pac-Soo CK, Maze M, Ma D. Nociceptive stimuli enhance anesthetic-induced neuroapoptosis in the rat developing brain. Neurobiol Dis. 2012; 45:743–50. [PubMed: 22075165]
16. Pan C, Xu Z, Dong Y, Zhang Y, Zhang J, McAuliffe S, Yue Y, Li T, Xie Z. The potential dual effects of anesthetic isoflurane on hypoxia-induced caspase-3 activation and increases in β-site

amyloid precursor protein-cleaving enzyme levels. Anesth Analg. 2011; 113:145–52. [PubMed: 21519046]

17. Xu Z, Dong Y, Wu X, Zhang J, McAuliffe S, Pan C, Zhang Y, Ichinose F, Yue Y, Xie Z. The potential dual effects of anesthetic isoflurane on Aβ-induced apoptosis. Curr Alzheimer Res. 2011; 8:741–52. [PubMed: 21244349]